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ETIOLOGIC AND PATHOLOGIC FACTORS IN POLYCYTHEMIA VERA. By PAUL REZNIKOFF, M.D., NATHAN CHANDLER FOOT, M.D., and JAMES M. BETHEA, M.D. . 753

MACROCYTIC ANEMIA WITH APLASTIC FEATURES FOLLOWING THE APPLICATION OF SYNTHETIC ORGANIC HAIR DYE. By C. W. BALDRIDGE, M.D. 759

THE NEUROLOGIC ASPECT OF LEUKEMIA. By ROBERT S. SCHWAB, M.D., and SOMA WEISS, M.D. 766

FATAL ETHYLENE DICHLORID POISONING. By W. C. HUEPER, M.D., and CALEB SMITH, M.D. 778

SPINDLE CELL SARCOMA OF THE PANCREAS. By ERNST J. OESTERLIN, M.D., and ROBERT W. BLUMENTHAL, M.D. 784

CONGENITAL CYSTS OF THE LUNG. By JOHN P. SCOTT, M.D., and ARTHUR D. WALTZ, M.D. 788

FACTORS AFFECTING THE APPEARANCE AND DURATION OF GLYCOSURIA. By C. S. ROBINSON, PH.D., R. C. DERIVAUX, M.D., and BARBARA HEWELL, M.D. . . . 795

VARIATIONS IN BLOOD PRESSURE IN RENAL TUBERCULOSIS. By CARL G. MORLOCK, M.D., and BAYARD T. HORTON, M.D. 803

FACTORS CONDITIONING THE TRANSMISSION OF SYPHILIS BY BLOOD TRANSFUSION. By HUGH J. MORGAN 808

THE EARLY RESPONSE TO VENESECTION WITH OBSERVATIONS ON SO-CALLED BLOODLESS VENESECTION. By WILLIAM A. BRAMS, M.D., and J. S. GOLDEN, M.D. . 813

PAIN IN THROMBO-ANGIITIS OBLITERANS: A CLINICAL STUDY OF 100 CONSECUTIVE CASES. By GRACE A. GOLDSMITH, M.D., and GEORGE E. BROWN, M.D. . . . 819

THE FOUR-LEAD ELECTROCARDIOGRAM IN CORONARY SCLEROSIS. A STUDY OF A SERIES OF CONSECUTIVE PATIENTS. By A. BOHNING, M.D., and L. N. KATZ, M.D. 833

CORONARY THROMBOSIS AND ITS EFFECT ON THE SIZE OF THE HEART. By EMMET F. HORINE, M.D., and MORRIS M. WEISS, M.D. 858

INDEX TO PHYSICIAN'S SUPPLIES . . . . . ADV. PAGE 38

Contents continued on adv. page 10

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JUNE, 1935

ORIGINAL ARTICLES.

ETIOLOGIC AND PATHOLOGIC FACTORS IN POLYCYTHEMIA VERA.

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Polycythemia vera, first described by Vaquez[1] in 1892 and clearly defined by Osler[2] in 1903, has presented several puzzling features to medical investigators. In all the contributions which have been made in this field many suggestions have been offered to explain the pathogenesis of the condition, but none has served to clarify the problem in spite of the fact that the pathologic physiology of polycythemia associated with pulmonary and cardiac lesions and with the response to an environment found at high altitudes is understood. Excellent summaries of our knowledge of polycythemia, both primary and secondary, have been written by Weber[3,4] and by Harrop.[5]

This report has for its object the presentation of a few observations which may throw some light on the mechanism involved in polycythemia vera and have not been emphasized previously.

In the Hematology Clinic of the New York Hospital it has been noticed that the majority of patients under treatment at present for polycythemia vera were Jews born in eastern Europe (Russia, including Ukrainia, Poland, Austria, Lithuania, Roumania, Czechoslovakia). This suggested a similarity between polycythemia vera and thromboangiitis obliterans. Such a relationship was rendered more probable by the fact that many of the polycythemic patients came to the clinic complaining of symptoms referable to their peripheral vascular systems and were being treated for thromboangiitis obliterans as well as for polycythemia vera.

To study the racial and national incidence of polycythemia vera, the records of six institutions were investigated. These hospitals were selected because the general admission of eastern European Jews was not especially high and because the case histories permitted an accurate differentiation between polycythemia vera and polycythemia secondary to some other condition. The clinics were Bellevue Hospital, Cornell Clinic, New Haven Hospital, New York Hospital, Presbyterian Hospital and St. Luke's Hospital.* The criteria used to accept a diagnosis of polycythemia vera were a majority of the following: (*a*) Polycythemia which was distinct and persistent, and which returned after cessation of therapy; (*b*) splenomegaly; (*c*) typical red cyanotic appearance of patient; and (*d*) absence of any other distinct lesion such as pulmonary or cardiac, to explain the polycythemia. The records from the New Haven Hospital were not examined by us but were summarized by Dr. Theodore Klumpp.

TABLE 1.—RACIAL AND NATIONAL ORIGIN OF PATIENTS SUFFERING FROM POLYCYTHEMIA VERA.

Institutions.	Total No. of patients (polycythemia vera).	Patients of Jewish origin born in eastern Europe (polycythemia vera).		General admission of patients of Jewish origin born in eastern Europe.
		No.	%	%
Bellevue Hospital	28	14	50	3 (sample year)
Cornell Clinic	7	4	57	12 (estimate)
New York Hospital	19	12	63	9 (sample year)
Presbyterian Hospital	33	13	39	15 (race not given; eastern European birth)
St. Luke's Hospital	34	15	44	7 (race not given; eastern European birth)
New Haven Hospital	13	6	46	10 (estimate)
	134	64	47.8	9 (approximate)

The accompanying table gives the results obtained. It can be seen that in each clinic the incidence of polycythemia vera among eastern European Jews was distinctly high. The per cent of

* We wish to express our gratitude to Drs. Woodruff, Wyckoff, Nammack, Klumpp, Palmer and Wood for permission to study and quote from the records of these clinics.

patients from this group among the general clinic and hospital population could not be obtained in some institutions because such data were not kept. But as far as could be determined the average incidence of eastern European Jews among the general admissions in these hospitals was under 10%. The average incidence of eastern European Jews suffering from polycythemia vera was almost 48% and ranged from 39% to 63% for 134 patients.

The eastern European countries were circularized for information that might give some statistics dealing with the racial incidence of polycythemia. The only country which had any figures was Lithuania.[6] The population of this country is about 2,000,000, of which 155,000 (7.7%) are Jewish. Of 4 cases of polycythemia vera from 1930 to 1934, 2 were Jewish. Professor Julius Bauer[7] of the Allgemeine Poliklinik in Vienna informs us that, although he has no statistics available, he has the impression that polycythemia vera is more common in Jews. Dr. C. W. Baldridge[8] wrote us that in the last 13 years 10 polycythemic patients were treated by the State University of Iowa, Department of Medicine. None of these was Jewish, but the incidence of Jews in the general hospital population is very low and the incidence of foreign-born Jews is probably negligible.

The resemblance of the racial and national incidence of polycythemia vera to that of thromboangiitis obliterans naturally suggested that the bloodvessels of the bone marrow merited study. As far as we could determine no investigation of lesions of the bone marrow vessels has ever been reported. It was thought best to use Masson trichrome stains to obtain good pictures of the bloodvessels. Eosin azure and Giemsa stains were also used. A total number of 69 bone marrow specimens and 4 sections of bloodvessels from amputated limbs of patients suffering from thromboangiitis obliterans and arteriosclerosis were studied.* The bone marrow was obtained from the sternum in the case of biopsy specimens and from several sources in the case of autopsies, and in the most important cases was fixed in Zenker-formol or in neutral formalin. Of the 69 bone marrows studied 12 were biopsy specimens, of which 5 were from polycythemia vera patients; 2 were from secondary polycythemia (1 patient had pulmonary bronchiectasis and fibrosis, and 1 probably has splenic arteriosclerosis or so-called abdominal thromboangiitis obliterans); the rest from benzol poisoning, aplastic anemia and aleukemic leukosis. The remainder of the bone marrow sections was obtained from autopsy cases. Two of these were from polycythemia vera, 5 from agranulocytosis and the rest from a variety of patients including general arteriosclerosis, cardiac diseases, nephritis, senility, leukosis, malaria, pneumonia. The speci-

* We wish to thank Drs. Conway and Glenn for performing bone marrow biopsies, and Drs. Curphey, Trubek, Bishop, Olcott, Angevine, R. A. Moore, Helpern and Lawrence Smith for specimens.

mens were obtained from individuals of all ages ranging from infancy to people over 70 years.

The result of these bone marrow studies (see illustrations) showed that in all the polycythemia vera cases there was distinct thickening of the capillary walls and this increase was characterized by a distinct green stain with the Masson trichrome dye, indicating an increase in the fibrous tissue. It should be pointed out that the structures which are designated as capillaries are usually subarteriolar, although some of them may be very small venules because the latter structures have no musculature in the bone marrow. However, these vessels were compared with those of similar size in the control group and had the thinnest walls in the entire section. This capillary thickening was made more evident by the nuclei failing to protrude into the lumen, as is the case with normal vessels. All of the polycythemia bone marrows, except one, showed marked subintimal and adventitial fibrosis of the arteries and arterioles, and in the latter vessels some of the fibrosis extended into and through the media. In 3 of the 5 agranulocytic bone marrows there was some swelling of the capillary walls, but this seemed to be of an edematous nature rather than distinct fibrosis. All of the rest of the bone marrows showed no changes of this type. In the patients suffering from arterio- or arteriolarsclerosis the vessels showed principally medial and adventitial fibrosis; but the capillaries were normal in appearance except that there was a moderate increase of fibrous tissue around them in many cases. As has been pointed out elsewhere,[9] these polycythemic marrows also showed an increase in megalokaryocytes. One polycythemic bone marrow showed distinct thrombosis, both fresh and organized, of some small arteries. This was regarded as significant, since the capillaries in the thromboangiitis obliterans sections showed the same thickening and fibrosis as that seen in the polycythemic bone marrows. One of the most interesting bone marrow specimens was derived from a patient who had been suffering from polycythemia vera for a short time and was considered a mild case. His highest count was 6,500,000 red blood cells, his spleen was only moderately enlarged, he had pain in the calf of his right leg for only 4 months and he responded well to very small doses of acetylphenylhydrazin. Incidentally his brother had a well advanced polycythemic condition. A biopsy specimen of this man's bone marrow showed marked inflammatory and necrotic lesions along the course of his bloodvessels, characterized by a cellular exudate which formed perivascular "cuffs," and some of his capillaries demonstrated thickening in the midst of pronounced inflammatory lesions. The exudate consisted chiefly of lymphocytes and monocytes caught in the migratory elongated phase. A few neutrophils were occasionally found; these rarely formed miliary abscesses.

FIG. 1.—Artery in bone marrow of normal subject. Magnified × 280. Practically no fibrous tissue infiltration of wall of vessel.

FIG. 2.—Artery in periosteum of arteriosclerotic patient. Magnified × 280. Fibrous tissue infiltrating muscularis.

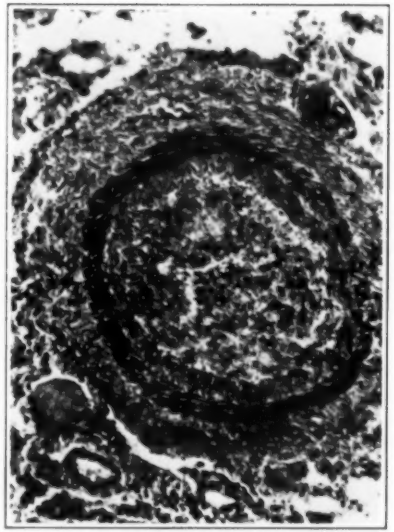

FIG. 3.—Artery in bone marrow of a polycythemic patient. Magnified × 110. Marked fibrosis of subintima and adventitia.

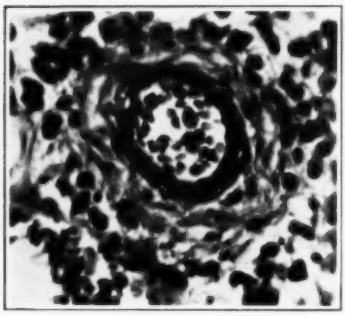

FIG. 4.—Arteriole in bone marrow of normal subject. Magnified × 270. No fibrosis in wall of vessel.

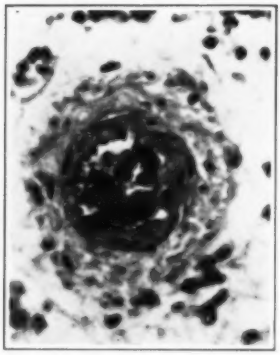

FIG. 5.—Arteriole in bone marrow of polycythemic patient. Magnified × 540. Fibrous tissue infiltrating entire wall of vessel.

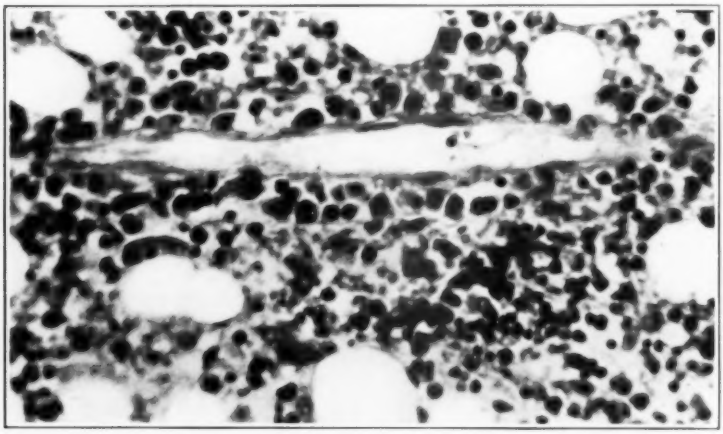

FIG. 6.—Capillary in bone marrow of normal subject. Magnified × 270. Thin wall, nuclei bellying into lumen.

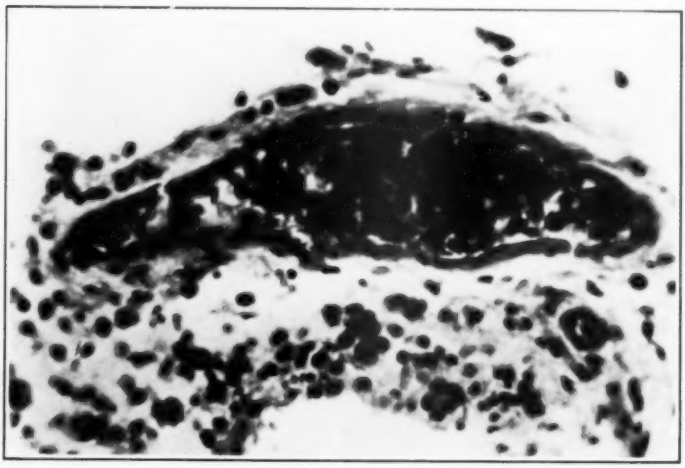

FIG. 7.—Capillary in bone marrow of polycythemic patient. Magnified × 290. Marked thickening of wall. Cross section of markedly thickened small capillary in field.

Comment. The significance of these observations may have various interpretations. As far as the racial and national incidence of polycythemia is concerned, the high incidence among Jews born in eastern Europe applies, of course, only to the cases presented in this study. Whether the same findings will hold true for any other large group of patients will depend upon future studies. However, it is interesting to note that Weber[10] states, "I am myself inclined to the opinion that polycythemia rubra, at all events 'polycythemia hypertonia' (which I regard as a secondary polycythemia), is rather more frequently met with amongst the Hebrew population of Europe than amongst other Europeans." In spite of the fact that Harrop[11] states that this disease is present in all races and has no regional distribution, its predominance in Jews is suggested by Lucas' studies[12] as well as McAlpin and Edsall's case reports.[13] Finally at the recent Congress of the International Association for Geographic Pathology at Utrecht, Professor Anitschkow analyzed 40,000 autopsy reports of arteriosclerosis and intimated that the only definite conclusions from such a study was that vascular sclerosis is probably more prevalent among Jews.[14]

The relationship of these vascular lesions in the bone marrow to polycythemia vera merits further study. It has been suggested that the vascular disease is secondary to the increased viscosity of the blood. Koga[15] describes such a condition in spontaneous gangrene of the extremities and Stern[16] claims that in Buerger's disease a high viscosity of the blood is not an unusual exception with a normal blood count. Schneider,[17] Dietl and Fritz[18] and Münzer[19] have noticed arteriolar and capillary lesions in polycythemia vera in various parts of the body, although they made no bone marrow studies, and suggested that these vascular lesions caused anoxemia of the tissues with secondary overcompensation of the bone marrow. Münzer feels that acute infections such as scarlet fever and typhus may cause general capillary disease. Although Brown, Allen and Mahorner[20] state that they have never seen any association between thromboangiitis obliterans and polycythemia vera, this is not the experience of our clinic, where we find a frequent association. Nor does one gather from Weber's case reports[21] that the combination is rare. In fact, Brown and Giffin[22] report that of 100 polycythemia vera patients, 27 complained of symptoms and demonstrated lesions referable to the extremities (excluding venous thrombosis); 20 were arteriosclerotic, 6 had vasomotor disturbances and 1 was definitely a case of thromboangiitis obliterans. Averbuck and Silbert[23] find that in thromboangiitis obliterans thrombosis of vessels other than the extremities is a very common occurrence.

Almost all students of this subject have been intrigued with the possible relationship of polycythemia vera to anoxemia. It is true that earlier workers[24] regarded this disease as analogous to leukemia.

But this is not generally considered probable because of the maturity of the red blood cells both in the bone marrow and in the peripheral blood. Some observers[25,26,27] considered infection as an important etiologic factor and some familial incidence has long been known. Without much evidence a hormonal defect has also been suggested but by far the most intensive work has concerned itself with the relationship of anoxemia to polycythemia. This is a logical concept because of the known relationship between these two conditions at high altitudes and in cardiac and pulmonary diseases. Harrop[28] suggested that there might be a reduced rate of diffusion of oxygen through the lung and reduced oxygen tension. He said, "If one may assume a very sluggish blood flow in the marrow—small differences in oxygen tension might assume great significance." He found, however, no lesion to account for possible anoxemia, and stated that the "time is ripe for a reinvestigation of the histological findings." Barach and McAlpin[29] believed that polycythemia is not due to anoxemia stimulus because 2 of their patients were kept in an environment of 50% oxygen for 2 weeks without showing any change in red blood cell count, hemoglobin or oxygen capacity. This is evidence against general anoxemia but does not rule out a possible localized anoxemia in the bone marrow. Weber[30] has presented the most interesting opinions, at least so far as this study is concerned. He says "all cases of erythraemia (so-called primary cases) are really only examples of *secondary* or *symptomatic* polycythemia occurring as a result of, or vital reaction towards, some unrecognized obstruction to the circulation of blood in the viscera. The clinical history in erythraemia sometimes furnishes evidence" (of conditions) "which are not unlikely to cause disease and degenerative changes in bloodvessels, leading to circulatory disturbance." "Erythraemia"—(is) "a primary myelopathic disease." The question might then well be raised whether the anoxemic state caused by vascular disease in the bone marrow itself may not be the initiator of compensatory or overcompensatory red blood cell production which results in polycythemia vera.

Conclusions. 1. Of 134 patients suffering from polycythemia vera about 48% were Jews born in eastern Europe. The records of these patients were obtained from six institutions in which the average incidence of this racial and national group was under 10%.

2. Seven bone marrow specimens from polycythemia vera patients showed distinct capillary thickening, probably fibrosis, and 6 of these showed in addition marked subintimal and adventitial fibrosis of the subarteriolar capillaries, arterioles and arteries. Of 62 control specimens only 3 of 5 agranulocytic bone marrows gave slight thickening of capillaries, probably due to edema. The rest showed no change from the normal. In the cases of general arterio- or arteriolarsclerosis, medial fibrosis was evident.

3. The vascular changes, especially in the capillaries, of the bone

marrow in polycythemia vera patients suggest the possibility that these lesions may result in anoxemia of the bone marrow with compensatory or excess compensatory polycythemia.

REFERENCES.

1. Vaquez, H.: Compt. rend. Soc. de biol., **44**, 384, 1892.
2. Osler, W.: Am. J. Med. Sci., **126**, 187, 1903.
3. Weber, F. P.: Erythrocytosis and Erythræmia (Vaquez-Osler Disease), H. K. Lewis & Co., Ltd., London, 1921.
4. Weber, F. P., and Bode, O. B.: Polycythæmia, Erythrocytosis and Erythræmia (Vaquez-Osler Syndrome), H. K. Lewis & Co., Ltd., London, 1929.
5. Harrop, G. A., Jr.: Medicine, **7**, 291, 1928.
6. Personal communication, Dr. Maciulis and Dr. Kotiluis, Division of Medicine, Department of Health, Ministry of Interior, Republic of Lithuania.
7. Personal communication.
8. Personal communication.
9. Askanazy, M.: Knochenmark, Handbuch der speziellen pathologischen Anatomie und Histologie, Henke, F., und Lubarsch, O., Julius Springer, Berlin, **1**, Pt. 2, 946, 1927.
10. Weber, F. P.: Erythrocytosis and Erythræmia (Vaquez-Osler Disease), H. K. Lewis & Co., Ltd., London, 1921, p. 45.
11. Harrop, G. A., Jr.: Medicine, **7**, 302, 1928.
12. Lucas, W. S.: Arch. Int. Med., **10**, 597, 1912.
13. McAlpin, K. R., and Edsall, K. S.: New York State J. Med., **33**, 1039, 1933.
14. Personal communication, Dr. Robert A. Moore.
15. Koga, G.: Deutsch. Ztschr. f. Chir., **121**, 371, 1913.
16. Stern, W. G.: J. Bone and Joint Surg., **6**, 902, 1924.
17. Schneider, P.: München. med. Wchnschr., **65**, 689, 1918.
18. Dietl, K., and Fritz, A.: Med. Klin., **17**, 749, 1921.
19. Münzer, E.: Wien. Arch. f. inn. Med., **2**, 1, 1921.
20. Brown, G., Allen, E. V., and Mahorner, H. R.: Thromboangiitis Obliterans, W. B. Saunders Company, Philadelphia, 1928.
21. Weber, F. P.: Erythrocytosis and Erythræmia (Vaquez-Osler Disease), H. K. Lewis & Co., Ltd., London, p. 79, 1921.
22. Brown, G. E., and Giffin, H. Z.: Arch. Int. Med., **46**, 705, 1930.
23. Averbuck, S. H., and Silbert, S.: Ibid., **54**, 436, 1934.
24. Minot, G. R., and Buckman, T. E.: Am. J. Med. Sci., **166**, 469, 1923.
25. Weintraud, W.: Ztschr. f. klin. Med., **55**, 91, 1904.
26. Gaisböck, F.: Ergebn. d. inn. Med. u. Kinderh., **21**, 204, 1922.
27. Gutzeit, K.: Deutsch. Arch. f. klin. Med., **141**, 30, 1923.
28. Harrop, G. A., Jr.: Medicine, **7**, 293, 321, 1928.
29. Barach, A. L., and McAlpin, K. R.: Am. J. Med. Sci., **185**, 178, 1933.
30. Weber, F. P.: Erythrocytosis and Erythræmia (Vaquez-Osler Disease), H. K. Lewis & Co., Ltd., London, pp. 122, 123, 1921.

(Titles have been omitted for sake of brevity.)

MACROCYTIC ANEMIA WITH APLASTIC FEATURES FOLLOWING THE APPLICATION OF SYNTHETIC ORGANIC HAIR DYE.

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Long before beauty culture became a "science," the ancient Persians used vegetable compounds as hair dye. Their methods

* Dr. Baldridge was unfortunately killed in an automobile accident shortly after submitting this manuscript, which has been revised by his colleague, Dr. W. M. Fowler.—The Editors.

proved to be too tedious and transient for us moderns, so that newer and incidentally more dangerous methods were devised. Physicians have not failed to condemn the use of most modern hair dyes, whether metallic, organic or "compound."[1] Paraphenylene-diamin, first prepared by Hoffman, in 1854, formed the key substance for most organic hair dyes until recently, although the use of this substance has been prohibited in some countries because of the skin reactions which it induced.[2]

Except for dermatitis, few intoxications attributable to hair dye have been described in the literature, although it is known that many anilin derivatives exert a deleterious effect on the blood-forming organs. Close[3] reported a case in which involvement of the nervous system was attributed to poisoning by a hair dye of the paraphenylene-diamin type, and Haldimann[4] a case in which anemia was apparently due to anilin poisoning.

We have not found any previously reported case in which macrocytic anemia was attributed to hair dye poisoning. Because cases of macrocytic anemia which do not respond to liver therapy are encountered occasionally, the present report is believed to be timely.

The following cases were observed in a period of about 7 months, December, 1933, to July, 1934:

Case Abstracts. Case 1.—M. M., a married woman, aged 42, felt fatigued during 1933, and gradually lost from 167 to 147 pounds in weight. She had dyed her hair in 1932 and had repeated the procedure about 15 times. In October, 1933, she had her hair dyed and a permanent wave put in on the same day. Later in October she began to notice slight bleeding from the nose. From November 16 to 28 the epistaxes were frequent and severe and accompanied by fever, weakness and pallor. After local treatment failed to control the hemorrhages her physician administered horse serum, fibrinogen and calcium gluconate and finally transfusions of 400 cc. of citrated blood were given on each of the 4 days, from November 28 to December 1, 1933. In spite of all treatment the bleeding from the nose continued, and in addition purpuric spots, uterine and urinary bleeding developed.

The patient was admitted to the University Hospital, December 5. There was marked pallor without icterus, the nose was bleeding and crusted, the tonsillar regions were ulcerated and petechiæ and ecchymoses were noted over the body. The spleen was not palpable at the time of admission, but a week later the edge could be felt. The lymph nodes were not enlarged and the gums were not hypertrophied. The cardiovascular, respiratory and nervous systems were normal. There was vaginal bleeding and urine obtained by catheter was frankly bloody. The stool was dark and gave a strongly positive test for occult blood.

Examination of the blood revealed: Hemoglobin, 28%, or 4 gm. per 100 cc. (Newcomer); erythrocytes, 1,650,000 per c.mm.; hematocrit, 13.5%; color index, 0.8; volume index, 0.94; saturation index, 0.9;[5] leukocytes, 2550 per c.mm. Differential count: Neutrophils, 46% (band forms, 19; two lobes, 15; three lobes, 12); lymphocytes, 38%; monocytes, 13%; degenerated cells, 3%. The neutrophils all contained toxic granules and some were vacuolated. The erythrocytes varied in size from 5 to 14 microns (ocular micrometer disk). No attempt was made to ascertain the average

diameter of erythrocytes because of marked poikilocytosis and because of the recent transfusions. There was diffuse polychromasia but no stippling was found. The bleeding time was more than 25 minutes; the capillary resistance test was positive; the clot was non-retractile and the platelets measured 0.02% by volume. The coagulation time was 5 minutes and hemolysis of erythrocytes began in 0.42 and was complete in 0.32% sodium chlorid solution. Reticulocytes made up 1.6% of the erythrocytes. The plasma fibrinogen was 0.34%; plasma albumin, 2.28% and plasma globulin 2.1%. The blood calcium was 9.8 mg. per 100 cc. and the van den Bergh was 0.8 mg. per 100 cc. (indirect). The gastric juice was not examined. Roentgenograms of the skull and pelvis were normal. The blood Wassermann reaction was negative.

Bone marrow removed from the upper tibia and suspended in serum suggested a paucity of cells. Neutrophils were virtually absent while myelocytes, myeloblasts and erythroblasts were very scarce.

The findings were those of a severe aplastic anemia and secondary hemorrhagic purpura. The patient was given 1100 cc. of blood as well as daily injections of 5 cc. of coagulen (Ciba). The hemorrhagic tendencies ceased and her recovery in the hospital was slow and uneventful. Hair dye had not been applied since October, 1933, and while I have not had an opportunity to examine the patient's blood since January, 1934, word was received on April 5, 1934, that she was improving steadily. She has since been lost sight of.

The history of the patient was explored exhaustively for exposure to substances which might produce such an aplastic anemia but no probable cause other than hair dye could be found. The patient had applied the dye herself the first time but the results were not satisfactory. She then had several applications of another dye and for the last two or three applications a third dye had been used. The Bureau of Investigation of the American Medical Association informed us that the second dye which the patient used contained paraphenylene-diamin, but that this was not an ingredient of the dye which was applied just before the permanent wave. The same company manufactured both of the latter two dyes and their representative confirmed the above facts concerning paraphenylene-diamin but refused to tell the formulæ for the dyes on the basis that they were trade secrets. Because the dyes almost surely contained anilin derivatives, it was felt that they might be toxic to the blood-forming organs. The changes in the erythrocytes were very suggestive of pernicious anemia but there was no shift to the right in the neutrophils and the patient recovered without liver therapy. There was no history of previous relapses nor paresthesias and no evidence of posterolateral sclerosis nor changes in the tongue.

Case 2.—A. B., a white woman, aged 47, was married at 19, had a spontaneous abortion at 22 and was divorced at 31. A subtotal thyroidectomy was done at the age of 33, but she entered the University Hospital when she was 43 because of a recurrence of the goiter. Another thyroidectomy was done and in addition a diagnosis of tabes dorsalis with gastric crises was made. From August, 1930, to September, 1932, the patient was admitted to the hospital 4 times and received 13 injections of neoarsphenamin (0.6 gm. each), 6 gm. of tryparsimid and about 30 injections of bismuth. She was inoculated with malaria but had only one chill. During these 2 years blood counts were made on 4 occasions with essentially normal findings. There were no further admissions to the hospital and no more blood counts until 1934, but between September, 1932, and January, 1934, about 60 injections of bismuth were administered by her home physician.

She dyed her hair continually from 1920 to 1934. At first the dye was applied every 3 or 4 months, but the interval between applications was

gradually decreased to 2 months. Permanent waves were never applied until 1930. Once in the summer of 1933 and again in March, 1934, permanent waves were applied a few days after the hair was dyed.

About May 1, 1934, the patient was examined elsewhere and was found to have a macrocytic anemia. The hemoglobin was found to be 70%; erythrocytes, 3,000,000; leukocytes, 5000. Free acid was present in the stomach only after the administration of histamin.

The patient reëntered the University Hospital, July 9, 1934, complaining of pain in her back, epigastric distress and weakness. The manifestations of tabes dorsalis with gastric crises, syphilis of the aorta, arterial hypertension (blood pressure, 190/120) and a small uterine fibroid were still present, but in addition there was a macrocytic anemia.

Blood examination revealed: Hemoglobin, 55%, or 7.8 gm. per 100 cc. (Newcomer); erythrocytes, 2,900,000; hematocrit, 34%; color index, 0.95; volume index, 1.3; saturation index, 0.7; leukocytes, 700 per c.mm. Differential count: Neutrophils, 50% (band forms, 6; two lobes, 33; three lobes, 10; four lobes, 1); lymphocytes, 23%; monocytes, 12%; eosinophils, 2%; degenerated cells, 13%. The neutrophils contained very few toxic granules. The erythrocytes varied from 7 to 12 microns in diameter (micrometer disk), averaging 9 microns. There was some poikilocytosis and slight polychromasia. Most of the macrocytes were hyperchromic. The appearance of the blood smear was very suggestive of pernicious anemia, except that there was no shift to the right in the neutrophils. The bleeding time was 4 minutes, the capillary resistance test slightly positive, the clot retracted poorly and the platelets were 0.1% by volume. The coagulation time was 7 minutes and hemolysis of erythrocytes began in 0.42% and was complete in 0.32% sodium chlorid solution. Reticulocytes made up 0.5% of the erythrocytes. The van den Bergh was 0.2 mg. per 100 cc. (indirect). Free acid was again present in the stomach after stimulation with histamin.

The patient was given 39 cc. of Lederle's liver extract intramuscularly over a period of 8 days, during which time the daily reticulocyte percentages were as follows: 1.8, 1.2, 1.4, 1, 1.2, 0.6, 0.8 and 0.8. There was no change in either the hematocrit or hemoglobin values after this amount of liver therapy. In February, 1935, her physician reported that she was improved and doing satisfactorily.

A review of the patient's subjective and objective symptoms shows that there were no previous relapses, no paresthesia, no posterolateral sclerosis, no tongue changes, no increase in serum bilirubin and the stomach was capable of secreting hydrochloric acid. The blood examination revealed anemia, leukopenia, a fairly high color index and macrocytosis. There was no response to liver extract.

Case 3.—B. B., a divorced woman, aged 45, complained of uncertainty in walking, pains in the legs and a girdle sensation around the lower abdomen. She was admitted to the University Hospital, July 20, 1934. The legs were both spastic and ataxic to such an extent that the patient could not walk alone. Two-point discrimination and vibratory senses were greatly decreased in the legs. Plantar extension was present on both sides. The left hand was awkward, the speech tremulous and there was slight euphoria. Dr. Van Epps, of the Department of Neurology, thought that the neurologic changes were more suggestive of multiple sclerosis than subacute combined sclerosis, in spite of the fact that the patient was found to have anemia of the macrocytic type and complete achlorhydria. The patient's blood and spinal fluid gave negative Wassermann reactions but her husband had had a strongly positive Wassermann test. She had had no antisyphilitic treatment.

The hair was dyed first, February 28, 1934, and again in April and in

June. The brand of dye was the same as that which had been used last by Case 1. A permanent wave had been done about 4 hours after the dye was first applied, in February. Shortly after this time the patient noticed that she was becoming pale. All of the neurologic symptoms, except a vague sense of uncertainty on a certain flight of stairs, appeared after the hair was dyed.

Examination of the blood revealed: Hemoglobin, 69% (9.8 gm. per 100 cc.); erythrocytes, 3,070,000 per c.mm.; hematocrit, 35%; color index, 1.1; volume index, 1.3; saturation index, 0.95; leukocytes, 5100 per c.mm. Differential count: Neutrophils, 60% (band forms, 13; two lobes, 26; three lobes, 17; four lobes, 4); lymphocytes, 24%; monocytes, 7%; eosinophils, 1%; basophils, 1%; degenerated cells, 7%. The neutrophils contained only a few toxic granules. The erythrocytes varied from 8 to 12 microns in diameter, the average being 9.5 microns. There was some poikilocytosis and slight polychromasia. Hyperchromia was the rule. After a careful search 1 neutrophil with 7 lobes in the nucleus was found. The changes noted in the smear were typically those of pernicious anemia. The bleeding time was 1 minute, the coagulation time was 4 minutes, the capillary resistance test was negative, the fragility of erythrocytes was normal, the clot retracted and the platelets were 0.5% by volume. The stomach contained no free hydrochloric acid, even after the administration of histamin. The van den Bergh reaction was indirect, 0.4 mg., and bilirubin per 100 cc. of blood

The patient was given 6 cc. of Lederle's liver extract intramuscularly daily for 20 doses. The daily reticulocyte counts with 2 control counts were as follows: 1.2, 1.4, 1.4, 1.5, 1.4, 1.9, 2.3, 2.6, 2.1, 1.6, 2.2, 1.8, 2.2, 2.1, 2, 1.9, 1.3, 1.5, 1.2, 1.1 and 1.9. The hemoglobin and hematocrit values were unchanged after the liver extract but the erythrocyte count had increased to 3,800,000, and the patient felt better. In February, 1935, her physician reported that she was improved and doing satisfactorily.

A review of the patient's subjective and objective symptoms shows that there were no previous relapses, no tongue changes and no increase in serum bilirubin. There were, however, paresthesia, posterolateral sclerosis, anemia, high color index, macrocytosis, leukopenia and achlorhydria.

Comment. The first patient was regarded as a probable instance of chemical poisoning for the following reasons:

1. There had been a profound decrease in erythrocytes, platelets and granulocytes with relative increase in monocytes. We had previously noted these changes in a case of chronic benzin poisoning.[6]

2. The hair dye was the most likely source of poisoning elicited.

3. Biopsy of the bone marrow, Roentgen ray and other examinations sufficed to exclude aleukemic myelosis, metastatic tumor of the bone marrow and other causes for myelophthisic or hemolytic anemia.

4. The fact that the patient recovered is perhaps the most conclusive evidence that the anemia and thrombopenia were not myelophthisic in origin. A diagnosis of pernicious anemia was never seriously considered even though the anemia was essentially macrocytic in type.

The permanent wave was applied to this patient on the same day that the hair was dyed the last time. One wonders if the heat and the ammonia water, which are used in the permanent wave process,

might either change the dye chemically or by the induction of hyperemia of the scalp, lead to its absorption in unusual amounts. A preparation which the patient used for washing hair was found to contain tartaric acid and an anilin dye.

Case 2 presents features which add materially to the belief that poisoning by hair dye may produce a macrocytic anemia. The company that manufactured the dye which was used by this patient gave the following information to the Bureau of Investigation of the American Medical Association in 1927. The dye contains no lead, silver or iron and no pyrogallol or paraphenylene-diamin. "The color base is toluylene-diamin, which in the preparation of the dye is so treated and combined with other ingredients in the manufacture as to safeguard, as fully as chemical science is at this time able to do, against possible skin irritation." A representative of this company informed us that no complaint of anemia following the use of their dye had been reported. Intoxication of the bone marrow by syphilis, mercury, bismuth or neoarsphenamin must be considered among the possible causes of the anemia from which this patient suffered. The patient had not received neoarsphenamin for 19 months before the anemia was discovered and the blood count was normal 18 days after the last administration of the drug. Bismuth and mercury are certainly not very likely to destroy hematopoietic tissue. Even if syphilis might produce a blood picture such as was seen in this patient, the changes would not be expected to develop during treatment.

The decreased volume of platelets and the slight neutropenia are noteworthy features, especially in view of the findings in Case 1. The blood findings resemble pernicious anemia more than any other hematologic disease. However, this diagnosis appears to be entirely untenable because of the presence of hydrochloric acid in the stomach, the absence of response to liver extract, the absence of posterolateral sclerosis, tongue changes, remissions, paresthesia and increased serum bilirubin.

The likelihood of pernicious anemia is much greater in Case 3 than in the other cases. While complete achlorhydria is not rare in anemic women of 45, it nevertheless should suggest the possibility of the anemia being pernicious in type. The presence of posterolateral sclerosis even though atypical in some respects would also point to the syndrome of pernicious anemia. In addition to these, we have changes in the blood which are entirely compatible with a diagnosis of pernicious anemia. The absence of tongue changes, the high platelet volume, the lack of increased bilirubinemia and the lack of a characteristic response to liver extract are points against this diagnosis. The reticulocyte count was higher both before and after 20 days of intensive treatment than is usually the case in pernicious anemia. The highest reticulocyte count (2.6%) occurred on the seventh day of liver therapy. This represented an increase of only 1.2 to 1.4% over the control counts.

If this had been a case of pernicious anemia, the expected reticulocyte count, according to Riddle's[7] table, would have reached 3.9% following oral administration of liver. The liver extract was given intramuscularly in order that the reticulocyte response might be as prompt and as pronounced as possible. No attempt was made to determine the presence or absence of Castle's factor in the gastric secretion of this patient. There is still doubt concerning the interpretation of the neurologic changes. It is to be recalled that the symptoms in this patient appeared shortly after the use of the hair dye and that Close[3] reported a case in which there was marked ataxia following the use of a similar dye. His patient recovered after discontinuing the use of the dye.

It is essential that more cases be studied in order to determine the exact relationship between the dye and the blood changes. Likewise, such observation should determine whether or not the changes in the blood and nervous system represent the usual reaction or a form of idiosyncrasy. The part played by the permanent wave must also be established.

It should be remembered that patients with pernicious anemia are likely to lose pigment from the hair at an early age, so that they have this added cause for using hair dye. Therefore, the presence of a macrocytic anemia in a patient with dyed hair does not establish a relationship between the two conditions.

It is possible that the substance which caused the anemia was not the original chemical compound which was applied to the hair, but rather some product which resulted from heating the initial compound. This, together with the fact that animal experimentation is so often confusing when applied to drug idiosyncrasies, or even to ordinary intoxications, has led me to report these cases without attempting to gain laboratory support for the view suggested. Also the opportunity to study human cases is almost unlimited, since a representative of one of the companies states that "thousands of such dual applications (dye and permanent waves) are occurring all over the United States every day."

Summary. Three cases of macrocytic anemia are described and discussed in women who had dyed their hair just before the application of permanent waves. In 1 of these the temporary changes in the blood were typical of aplastic anemia.

REFERENCES.

1. McCafferty, L. K.: Hair Dyes and Their Toxic Effects, Arch. Dermat. and Syph., **14**, 136, 1926.
2. Cole, H. N.: Dermatoses Due to Cosmetics, J. Am. Med. Assn., **82**, 1909, 1924.
3. Close, W. J.: Poisoning From Hair Dye, Med. J. Australia, **1**, 59, 1932.
4. Haldimann, J.: Severe Aplastic Anemia Resulting From Chronic Anilin Intoxication, Schweiz. med. Wchnschr., **59**, 838, 1929.
5. Osgood, E. E., and Hoskins, H. D.: Laboratory Diagnosis, Philadelphia, P. Blakiston's Sons & Co., p. 370, 1931.
6. Rohner, F. J., Baldridge, C. W., and Hansmann, G. H.: Chronic Benzene Poisoning, Arch. Path. and Lab. Med., **1**, 221, 1926.
7. Riddle, M. C.: Blood Regeneration in Pernicious Anemia During Early Remission, Arch. Int. Med., **46**, 417, 1930.

THE NEUROLOGIC ASPECT OF LEUKEMIA.

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Involvement of the central nervous system in leukemia is thought to be a rather unusual complication. In some of the standard textbooks of medicine, neurology, and pathology it is mentioned as rare, and in others it is not described. The purpose of this communication, in addition to reporting a case of lymphatic leukemia with an unusual presenting neurologic picture, is to show that the central nervous system is involved frequently, if not in nearly all cases of leukemia, and that such involvement results in clinical signs and symptoms which are frequently overlooked. We believe that the significance of the involvement of the central nervous system in the clinical course of leukemia is comparable in many respects to that in pernicious anemia and plumbism.

The general subject of the neurologic aspect of leukemia and an analysis of 334 cases of leukemia will be discussed after the case report.

Case Report. G. K., a 24-year-old married, American fuel oil deliveryman whose past, family, social and occupational histories were entirely irrelevant and uneventful, entered the Boston City Hospital on March 12, 1934 because of difficulty in swallowing of 2 days' duration. Four weeks previously he struck his right shoulder against a truck, which resulted in a stiff and painful upper arm for a week and a residual lameness. Eight days before entry he noted weakness of the left side of the face. In 2 days there was a complete paralysis of this side of the face and loss of taste. For 2 days before entering the hospital he had difficulty in swallowing solid foods. There was nothing else of importance in the history.

Physical Examination. A well-developed and well-nourished young male in no pain or distress; alert, intelligent and coöperative. His color was good and there was no fever. The first six cranial nerves were normal. The visual fields, the ophthalmologic examination and visual acuity were within normal limits. There was, however, a complete paralysis of the left seventh nerve involving the forehead, and some weakness of the left palate with an absent gag reflex. No further abnormality in the cranial nerves was noted. The act of swallowing appeared normal. The throat was slightly red, and there was a postnasal discharge. The rest of the physical and neurologic examinations, including a detailed examination of the lymphatic and sensory systems, was entirely within normal limits. The systolic blood pressure was 110 mm. Hg; diastolic, 80.

The white blood count on entry was 14,000; the red blood count, 5,000,000

per c.mm., and the hemoglobin, 95% (Sahli). The differential count showed: neutrophils, 52%; lymphocytes, 40%; monocytes, 4%; eosinophils, 2%. Both the white and the red blood cells appeared normal and there was nothing on repeated examinations to suggest disease in the blood-forming organs. Urine, stool, sputum, throat culture, blood Wassermann, and blood chemistry showed no abnormality.

The patient was thought to be suffering from a left-sided Bell's palsy, but because of the history of difficulty in swallowing and the weakness of the left ninth nerve, a bulbar type of poliomyelitis was also considered.

Course. On the 3d day the white blood count had increased to 19,000 without any change in the character of the white cells or in the neurologic or physical condition. Fever was not present. A lumbar puncture was now performed, with the patient well relaxed and lying on his side. A ground-glass, colorless fluid was obtained at a pressure of 150 mm. of water. Dynamics of the spinal fluid were in all respects normal. The fluid contained 1900 lymphocytes per c.mm., and 170 mg. of protein per 100 cc. The chlorid and sugar contents were quantitatively within normal limits. There was a strong midzone rise in the colloidal gold curve. The Wassermann test and the cultures of the spinal fluid were negative. On the 4th day the right seventh nerve became involved, and the patient showed a typical facial diplegia. Symptomatically he was unchanged.

Beginning on the 5th day the patient showed improvement clinically, in that the facial diplegia, together with the weakness of the ninth nerve, gradually cleared. The sensation of taste had returned at the end of the first week and an electrical sensory examination of the tongue was within normal limits. The leukocytosis in the blood persisted, on the other hand, as did the pleocytosis in the spinal fluid. The high-protein content of the cerebrospinal fluid continued, and pressures of from 200 to 250 mm. of water were frequently encountered. The details of the blood and the spinal fluid findings and their relationship are presented in Table 1 and Chart I. Notwithstanding the fact that the patient felt well, had a good appetite and had no fever, a complete neurologic examination was done every day.

On the 10th day the patient exhibited clinical signs of cerebral hypotension: headache, stiff neck, vomiting and a spinal fluid pressure of less than 10 mm. of water. It was thought that the frequent punctures and the need of large amounts of fluid at each tap for the tests had brought on this condition. The syndrome was successfully overcome in a day or two by raising the foot of the patient's bed, forcing fluids by mouth, administering pituitrin intramuscularly and discontinuing the lumbar punctures for 10 days.

On the 33d day the patient walked about his room, feeling perfectly well. The physical and neurologic examinations revealed normal findings except for very slight residual facial diplegia. The blood findings, however, were now suggestive of an early leukemia: hemoglobin, 62%; red blood cells, 3,500,000; white blood cells, 21,000 per c.mm. The differential count showed: neutrophils, 28%, of which 6% were stab forms; lymphocytes, 40%; atypical lymphocytes, 5%; monocytes, 4%; eosinophils, 3%; "blasts," 6%; myelocytes, 7%; nucleated red cells, 4%. There was anisocytosis but very little poikilocytosis or polychromatophilia. Although the basal metabolism was only +3%, the metabolism of the sterile blood (measuring the oxygen consumption of the cells during 24 hours in an incubator) was +23%, as compared with that of two normal subjects, which is also suggestive of a leukemic blood. The spinal fluid at this time showed 400 lymphocytes, a high-protein content, and a normal pressure. On the patient's insistence he was temporarily discharged home for a period of 2 weeks, with the probable diagnosis of leukemia.

At home he was symptomless for 1 week and then developed a severe

headache, vomiting and general malaise. He returned on the 60th day after his first admission, presenting the following clinical picture: There was evidence of loss of weight, and pallor. The fundi showed very full veins, but there were no hemorrhages nor choking of the disks. Except for

TABLE 1.—CHARACTERISTICS OF SPINAL FLUID AND OF BLOOD IN CASE REPORTED.

Day of illness.	Spinal fluid.							Blood.		
	Pressure, mm. H_2O.	Protein, mg. per 100 cc.	Sugar, mg. per 100 cc.	Chlorid, mg. per 100 cc.	Colloidal gold curve.	White blood cells, per c.mm.	Red blood cells, per c.mm.	White blood cells, thous. per c.mm.	Red blood cells, mills. per c.mm	Hemoglobin (Sahli), per cent.
				First	*Admission.*					
4	150	174	..	...	....	1,900	0	18.0	5.0	95
5	250	95	60	689	001233200	1,475	0	16.5		
6	220	91	..	...	....	560	0	17.5		
7	200	126	..	...	....	1,200	0	18.0		
8	160	136	59	687	0001221100	1,205	0	19.0		
9	70	118	..	...	....	2,500	0	22.0	5.0	90
11	80	116	..	...	....	1,900	0	19.0		
15	65	...	..	...	....	1,000	0	16.0		
19	0	...	..	...	....	1,200	300	17.0		
34	130	98	50	689	....	280	0	15.0		
39	230	...	..	...	....	410	0	23.0		
42	160	...	..	...	....	600	0	18.0	4.3	62
				Second	*Admission.*					
61	210	426	63	675	0022344321	4,500	200	20.0	3.0	56
63	215	384	..	...	....	4,200	250	22.0		
64	310	420	..	...	....	5,200	200			
65	250	522	33	633	....	5,000	1,000	26.0		
66	250	522	..	...	....	6,200	7,000	22.0		
67	280	402	..	...	....	6,200	2,000	32.0	2.0	45
68	250	462	55	678	....	5,000	2,000	27.0		
70	275	438	..	...	....	4,500	950	23.0		
72	250	214	77	658	0111232211	4,000	55,000	20.0		
73	280	243	..	...	....	10,000	56,000	13.0		
74	240	190								
74	170	240	..	...	....	8,000	90,000	8.9	2.3	37
75	270	170	..	...	....	2,000	12,000	5.9		
76	340	108	..	...	....	1,000	1,750	2.3		
77	210	108	78	684	....	500	4,000	1.8	2.0	30
78	300	78	..	...	....	500	2,500	1.7		
79	210	110	..	...	....	40	2,000	2.0		
80	270	106	74	677	0001211000	12	350	1.9		
81	150	106	..	...	....	15	350	2.3		
83	150	106	..	...	....	7	400	3.0		
88	180	132	..	...	....	4	20	10.0		
93	170	130	..	...	....	36	2	22.0	3.2	51
95	180	120	62	690	0112332110	39	0	29.0		
100	165	146	..	...	....	78	0	34.0		
106	170	196	..	...	....	220	0	35.0	2.1	36
111	190	196	..	...	....	270	0	31.4		
120	160	104	..	...	....	30	0	45.0	1.6	30
133	220	...	75	702	2334432110	75	0	30.0		

a faint residual weakness of the left seventh nerve, the cranial nerves were without abnormality. The neck was slightly stiff and there was a suggestive Kernig's sign. There was no adenopathy and the spleen was not palpable. The rest of the examination was within normal limits except for an absent right knee-jerk, even on good reinforcement, and generally sluggish reflexes, possibly due to mild acidosis from vomiting. There was no fever.

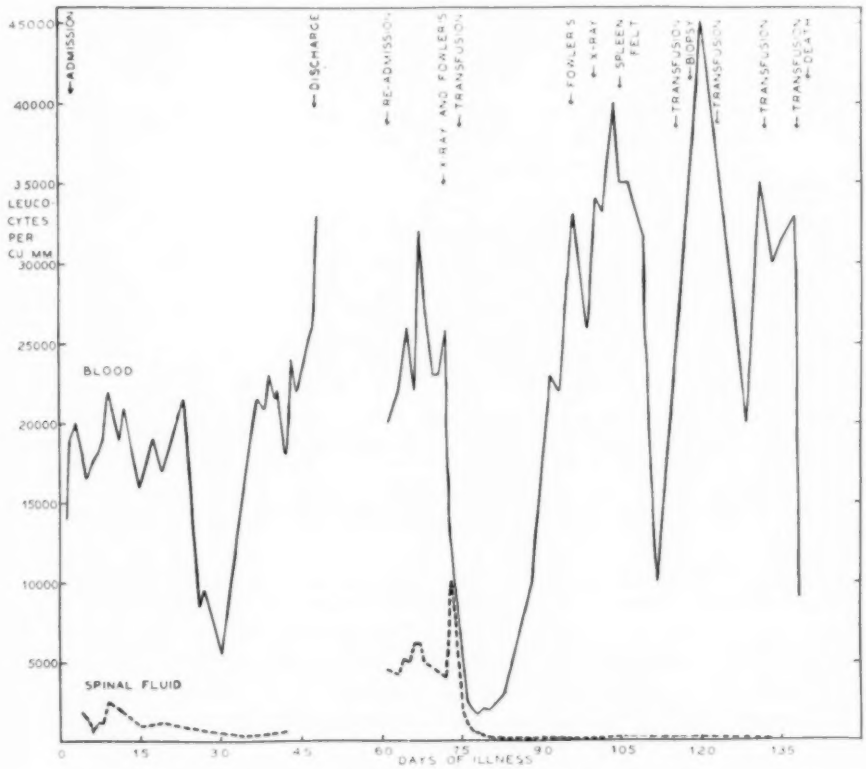

CHART I.—Relation of white cells in blood and spinal fluid in reported case.

The red count of the blood was 3,000,000; the hemoglobin, 56%, and the white count, 20,000. The differential count showed: neutrophils, 13%; lymphocytes, 63%; atypical lymphocytes, 11%; "blasts," 7%; myelocytes, 1%; eosinophils, 2%; nucleated red cells, 2%. Lumbar puncture, done within a few hours after admission, showed a ground-glass fluid containing 4500 cells, all of which were lymphocytes, and a protein content of 426 mg. per 100 cc. The pressure was 210 mm. of water. From this time on, lumbar punctures and blood studies were made almost daily (Table 1 and Chart I). At this time the *definite diagnosis* was made of leukemia, probably of the acute lymphatic type, with invasion of the meninges and cerebrum.

A second measurement of *blood metabolism revealed an elevated rate, but the basal metabolism of the patient was still normal.* The constant presence of 1000 to 2000 red cells in the spinal fluid during the first quarter of the second admission was the only hemorrhagic sign.

At this time observations were also made on the nature of the low sugar content of the spinal fluid. The comparative glycolytic power of sterile spinal fluid samples was measured. In one series the sugar content of the fluid after puncture was 65 mg. per 100 cc. The sugar content of the fluid which was kept for 24 hours in the incubator without thymol was 33 mg., and that with thymol was 40 mg. per 100 cc. The fluid kept for 24 hours in an icebox without thymol contained 55 mg. of sugar; the fluid from which the cells were centrifuged out and which was then kept for 24 hours in the incubator without thymol contained 63 mg. of sugar. Similar measurements of a second series revealed essentially identical findings, indicating that the low sugar content depended on the glycolytic power of the cells in the spinal fluid.

On the 72d day after the first admission, treatment was started with intravenous Fowler's solution in doses of 10 minims daily with an increment of 1 minim daily, and also deep Roentgen ray treatment over the base of the skull. The response was dramatic. For 2 days the number of cells in the blood slowly decreased, whereas the number of cells in the spinal fluid, both white and red, rose sharply (Chart I). Three days later, however, headaches and vomiting appeared, and the arsenic was discontinued. The next day the patient had a severe chill with a temperature of 102° F. Five days after beginning treatment the white blood count had reached a level of 3000 and there were only 500 white cells in the spinal fluid. Roentgen ray treatment was now discontinued and a transfusion of 500 cc. of citrated blood given, as the red cell count had fallen to 2,300,000 and the hemoglobin to 37%.

For the next 12 days the white cells in both the blood and the spinal fluid remained low; on the 87th day, however, the white cells in the blood began to rise again and in 4 days reached a level of 30,000, whereas the number of white cells in the spinal fluid remained between 25 and 50. The spinal fluid pressure was normal, and the protein content 125 mg. per c.mm. Fowler's solution was now given for 5 days without effect. After an interval of 4 days Roentgen ray therapy was again started, this time without effect. The spinal fluid continued to remain low in cells. Thereafter the patient ran a progressively downhill course.

By the 77th day the basal metabolism had reached a rate of +25%. Cervical and axillary adenopathy was revealed on the 86th day, and the spleen was first palpated on the 108th day. Petechial hemorrhages over the feet and legs, and tarry stools with diarrhea and painful rectum were observed on the 110th day. On the 122d day, for the first time, a crop of fresh retinal hemorrhages were seen in each fundus. On the same day the Roentgen ray plate was interpreted as showing periosteal changes in the orbits. All previous plates of the long bones, chest, pelvis, skull and orbits had been negative.

Roentgen ray treatment over the spleen was attempted, without benefit, on the 130th day. Four more transfusions were given between the 115th and the 138th days, in order to combat the progressive anemia, the red cell counts tending to fall below 1,500,000 and the hemoglobin to 25%. On the 135th day the patient developed a S. hemolyticus infection at the site of one of the transfusion cannula wounds. He began to bleed from the mouth and the renal tract, in addition to having bloody stools. The white blood count dropped terminally to 5000 lymphocytes, with less than 10% of the cells neutrophils, and these very toxic in appearance. No new neurologic signs developed, but there was a temperature of 102° to 103° F. Death followed 139 days after the first observation. The patient remained clear mentally to the end and seemed to die from exhaustion and hemorrhage.

Necropsy. A complete postmortem examination was done 1 hour after death (Dr. Robert Williams). The skin showed numerous purpuric spots

2 mm. in diameter and had a slight icteric tinge. There was no excess of fluid in the serous cavities, but the serous membranes in the three cavities were studded with pin-point hemorrhages. The heart was normal except for a small hemorrhage into the anterior cusp of the mitral valve. The lungs showed small hemorrhages at the posterior part of each base. The tracheal lymph nodes were slightly enlarged. The liver and spleen were enlarged. The esophagus and the stomach were normal, but the small and the large intestines, including the rectum, contained many pin-point hemorrhages. The kidneys had many small hemorrhages throughout their substance and there was bloody urine and fresh hemorrhages in the bladder. The brain and cord were grossly normal and each retina had several hemorrhages 1 to 2 mm. in diameter. The bone marrow was bright red.

Histologic Examination. Heart muscle and pericardium, lungs, bronchial walls and pleura were studded with small foci of very young, as well as mature lymphocytes. Similar foci were also found in the pancreas, kidneys, small and large bowels, rectum, spleen, liver, adrenals, lymph nodes, adventitia of the aorta, sternal and femoral marrow and skin. The eye showed similar infiltration of the optic nerve sheath, sclera and retina, in addition to many large and small hemorrhages in the retina. The meninges of the brain and cord were rather diffusely infiltrated with scattered foci of very young and of adult lymphocytes, but showed no sign of hemorrhage or of other type of meningeal reaction. The cerebral tissue itself contained scattered minute foci of very small lymphocytes without perivascular infiltration or hemorrhage. The cerebellum, remarkably, was free of change. Hematoxylin and eosin sections showed infiltrations of the posterior roots of the cord with young and with adult lymphocytes. The cord substance itself was normal except that in some areas occasional round cells were seen near the anterior roots. Oxidase stain of various tissues invaded with these cells showed that they were of the lymphocytic series. *The anatomic diagnosis was acute lymphocytic leukemia.*

Comment. The significance of the observations described in this case lies not only in the remarkable clinical features, but also in the fact that detailed clinical and laboratory observations were made from a relatively early stage of this disease to its termination. The unusual feature of this case was the early appearance of neurologic signs with remarkable changes in the spinal fluid before any abnormality could be ascertained in the appearance of the blood cells, in the spleen, the lymph nodes, or in the basal metabolic rate. Whether or not the nervous tissue was first involved it is not possible to state, as changes in the central nervous system might have caused more demonstrable clinical signs than changes in other organs.

It seems to us quite remarkable that there was no evidence of bleeding within the central nervous system, either clinically during the hemorrhagic phase or microscopically at postmortem.

The leptomeninges were probably the source of the lymphocytes in the spinal fluid, as they were the most prominently involved part of the nervous system at autopsy. The high spinal fluid protein is difficult to interpret. It will be shown later that abnormally high protein values are not infrequently found in the spinal fluids of cases of leukemia with central nervous system complications. Neoplastic tissue in contact with the pia-arachnoid is known to be the

source of very high protein content in the cerebrospinal fluid, and this is a valuable diagnostic aid in determining the presence of brain tumor. A similar mesodermal reaction which we believe to exist in leukemia might also raise the protein content considerably. The occasional low spinal fluid sugar values in this case are explained by the high glycolytic power of the leukemic cells in the fluid.

Clinical Manifestations of Involvement of the Central Nervous System in Leukemia. The literature on the subject of leukemia with central nervous system involvement includes, as far as we have been able to ascertain, 146 cases, reported by 75 authors (38 in German, 17 in American, 8 in English, 7 in French, 2 in Italian, 1 in Spanish, 1 in Swedish, and 1 in Russian literature). Since the first case described by the anatomist Burns in 1823[1] as a strange growth in the brain, probably a case of cerebral chloroma, the number of cases reported has steadily increased. Out of 38 cases of chloroma reported in the literature, Dock and Warthin, 1904,[2] found 13 cases with cerebral and spinal involvement, and to these they added 1 case of their own. Baudouin and Parturier, in 1910,[3] and Tapie and Cassar, in 1919,[4] gave excellent summaries of the French literature. In 1926 Fried[5] summarized 30 cases—mostly from the German literature—in addition to reporting 1 of his own. In 1927 Trömner and Wohlwill[6] reported careful microscopic examinations of the postmortem material from 12 cases of leukemia, 9 of which had manifested no neurologic signs or symptoms. They found, nevertheless, that 11 (91%) had microscopic evidence of invasion of the central nervous system. Ten of their cases showed invasion of the dura at the Gasserian ganglion; in only 1 case, however, was there a typical trigeminal neuralgia. These authors suggest that the fifth nerve should be tested in all cases of leukemia. Viets and Hunter, in 1933,[7] described 4 cases of lymphatic leukemia with involvement of the central nervous system. The spinal symptoms and pathology in leukemia were studied by Critchley and Greenfield,[8] in 1930. Diamond,[9] in 1934, published an excellent micropathologic study of 14 cases that he had examined, 7 of which showed no neurologic signs. In this paper Jaffé pointed out that leukemia does not involve the nervous system as a metastasis, but that the involvement represents the response of the neurologic mesoderm to a general disturbance of mesoderm throughout the body. The rest of the literature analyzed consisted chiefly in clinical and pathologic case reports combined with bibliographic references.

The type of neurologic lesion in the 146 cases reported in the literature, 89% of which came to postmortem examination, are presented in Table 2. The classification is based on the most significant presenting lesion, as found at postmortem, or as indicated by the clinical signs of those few cases without necropsy. In many of the cases (30%), however, more than one part of the nervous system was involved. The 23 cases with cranial nerve

palsies included 17 cases of seventh nerve paralysis with 12 instances of diplegia, and 7 cases of sixth nerve palsies with 5 diplegias. One of the 7 cases had both sixth and seventh nerve palsies. The eighth, ninth, tenth, eleventh and twelfth cranial nerves were the least frequently involved.

TABLE 2.—NEUROLOGIC LESIONS IN 146 CASES OF LEUKEMIA REPORTED IN THE LITERATURE.

Type of lesion.	No. of cases.	Per cent of total.
Cranial meninges	26	17.8
Cranial nerve nuclei	23	15.7
Cerebral invasion	23	15.7
Cerebral hemorrhage	47	32.2
Peripheral nerve	2	1.4
Spinal meninges	10	6.9
Spinal cord invasion	12	8.2
Spinal cord hemorrhage	1	0.7
Spinal extradural	2	1.4
Total	146	100.0

It is of special interest that the pathologic reports of Trömner and Wohlwill[6] and of Diamond[9] indicate that in leukemia a very high proportion of cases (over 90%) show microscopic involvement of the central nervous system. Between 50 and 75% of the cases, however, show no neurologic signs during life, suggesting that from 25 to 50% of all cases of leukemia should exhibit some clinical sign of neurologic involvement.

We have accordingly analyzed for neurologic signs and complaints the records of all the leukemia cases at the Boston City Hospital during the last 20 years (240 cases), at the Huntington Memorial Hospital during the last 10 years (67 cases), and at the Massachusetts General Hospital during the last 5 years (27 cases): a total of 334 cases. It was found that 20.5% had neurologic complications, excluding retinal lesions. It is to be regretted that in only 3.3% had postmortem examinations of the central nervous system been performed, and in none were careful serial sections made. It is impossible to classify the cases on an anatomic basis and to correlate the neurologic findings. We have grouped them according to the symptoms and signs. Tables 3 and 4 show the details of these find-

TABLE 3.—INVOLVEMENT OF THE NERVOUS SYSTEM IN 334 CASES OF LEUKEMIA RECORDED IN 3 BOSTON HOSPITALS.

	Number.	Per cent.
Total cases	334	
Postmortems	55	16.4
Postmortems of central nervous system	11	3.3
Involvement of central nervous system*	69	20.5
Retinal hemorrhage	38	11.4
Ophthalmoscopic examination	127	38.0

* These figures are based on clinical manifestations and do not include cases with retinal hemorrhage.

ings. It is of interest that the most frequent neurologic manifestations were cranial nerve palsies or anesthesias. Unilateral or bilateral involvements of the seventh and sixth nerves were most frequently encountered. It is probable that with greater appreciation of the neurologic complications in leukemia the incidence of neurologic symptoms and signs will be found to be higher than the 20.5% obtained from the records.

TABLE 4.—NEUROLOGIC SYMPTOMS AND SIGNS IN 69 CASES OF LEUKEMIA RECORDED IN 3 BOSTON HOSPITALS.

Clinical manifestations.	No. of cases.	Per cent of total.
Cranial nerve palsies or anesthesia	21	30
Absent reflexes	13	19
Pyramidal signs	8	12
Paresthesias	10	14
Herpes	4	6
Meningeal signs	5	7
Miscellaneous: Coma, paralysis, tremors	8	12
Total	69	100

In order to ascertain whether neurologic signs are more apt to occur in one form of leukemia than in another, the incidence of neurologic manifestations has been analyzed in the various types of leukemia of the Boston group of cases, as well as of the cases with neurologic involvement reported in the literature. Obviously, the classification of leukemias was not feasible in all instances; the latter group, as well as instances of chloromas, is included in the "miscellaneous group" of Table 5. The data presented in this table indicate that neurologic complications are apt to occur with about equal frequency in acute and in chronic forms of leukemia, as well as in lymphatic and in myelogenous types.

TABLE 5.—NEUROLOGIC INVOLVEMENT IN DIFFERENT TYPES OF LEUKEMIA.

Type of leukemia.	Total cases.		Involvement of central nervous system.		Retinal involvement.	
	No.	%.	No.	%.	No.	%.
Three Boston hospitals (334 cases)						
Acute lymphatic	62	18.5	14	22.6	14	22.6
Chronic lymphatic	80	23.9	17	21.2	8	10.0
Acute myelogenous	58	17.3	13	22.4	8	13.8
Chronic myelogenous	91	27.2	21	23.1	7	7.7
Miscellaneous group	43	12.9	4	9.3	1	2.3
Reported in literature (146 cases):						
Acute lymphatic	29	19.8	29	100.0		
Chronic lymphatic	17	11.6	17	100.0		
Acute myelogenous	21	14.4	21	100.0		
Chronic myelogenous	22	15.1	22	100.0		
Miscellaneous group (including 21 cases of chloroma)	57	39.0	57	100.0		

The Cerebrospinal Fluid in Leukemia. Little is known of the changes in the cerebrospinal fluid in leukemia, since in many of the cases reported in the literature lumbar punctures were not done. Of the 146 cases reported, only 23 had lumbar punctures and 1 a ventricular puncture (15.8%). Five of the 24 had two lumbar punctures, 1 had four, and 2 had combined cistern and lumbar punctures for leukemic spinal block. There are, therefore, in the literature altogether 35 examinations of specimens of spinal fluid. In none of these cases, however, was the fluid adequately studied. Of the 24 cases with spinal tap only 6 (25%) showed normal fluid with respect to pressure, protein and cell content. In 9 of the 24 cases (37.5%) there was an increase in the cellular elements. Hall's case of chloroma had 120 lymphocytes "per sixth field" but was described as cloudy.[10] In Hill's case the ventricular fluid contain 370 lymphocytes,[11] and in Barker's, 267 myelocytes.[12] Litterer reported a case with cloudy fluid with 80% myelocytes,[13] and Schwab a case with bloody fluid.[14] In the patient studied by Mieremet, the second tap revealed 34 lymphocytes.[15] Heissen's case had 375 myelocytes in the fluid of the first tap and none 10 days later.[16] Munro reported 4 taps on his case of meningeal leukemia with bloody fluid each time.[17] Viets observed 1 case of acute lymphatic leukemia with 750 lymphocytes and meningeal signs.[7]

In 10 cases there was increased protein qualitatively, as measured by the Pandy or Nonne-Apelt tests, and in 4 there was a quantitative increase—a total of 58.3%. Three of the 10 cases exhibited signs of block as a result of leukemic myelitis, but in 1 of these the fluid drawn from the cistern was, nevertheless, normal in protein. The spinal fluid pressure was high in 8 of the 24 cases, it was not mentioned in 4, and was normal in the rest. Bacterial cultures in 5 were negative. Sugar contents were normal in the 3 cases in which this test was done. No chlorid determinations were reported. Five cases showed midzone rises in the colloidal gold curve. The Wassermann reaction was negative in the 17 cases in which it was tested.

Among the 240 cases of leukemia at the Boston City Hospital there were 41 cases with signs referable to the central nervous system, excluding retinal hemorrhages. There were but 6 cases in which lumbar punctures were done (Table 6), not including the case here reported, in which repeated detailed studies of the spinal fluid were made. Of the total 7 cases with spinal tap, the fluid was entirely normal in 2, in 1 with active syphilis it contained 18 lymphocytes, and in 1 there were 500,000 red blood cells and a protein content of 524 mg. per 100 cc. The remaining 2 showed only high pressures with normal protein and cell contents. There was 1 additional case on which lumbar puncture was not done, but which at postmortem examination 4 hours after death showed 12,000 lymphocytes in the ventricular fluid. Control observations in postmortem spinal puncture showed only from 10 to 20 large cells.

TABLE 6.—SPINAL FLUIDS IN 10 CASES OF LEUKEMIA COLLECTED BY THE AUTHORS.*

No.	Type of leukemia.	Pressure, mm. H_2O.	Protein, mg. per 100 cc.	Cells (lympho-cytes), per c.mm.	Colloidal gold curve.
1	Chronic lymphatic	250	32	2	0000000000
2	Acute myelogenous	...	Negative	3	
3	Chronic myelogenous	320	28	0	0000000000
		250	32	0	0000000000
4	Acute myelogenous	...	18	0	0000000000
5	?	Normal	...	18	
6	Chronic myelogenous	Low	524 (Yellow)	500,000 (R. b. c.)	
7†	Acute lymphatic	200	120	500	2334432111
8	Chronic lymphatic	100	30	3	0000000000
9	Acute myelogenous	450	+++	22	5443322100
		450	110	12	
10	Acute myelogenous	80	+++	170	

* Cases 1 to 7 are from the Boston City, 8 and 9 from the Massachusetts General, and 10 from the Huntington Memorial Hospital.

† These figures represent the average of 40 lumbar punctures done on our reported case.

In the 67 cases of leukemia at the Collis P. Huntington Memorial Hospital during the last 10 years, one lumbar puncture was done in a case of meningeal leukemia. The spinal fluid showed 170 lymphocytes, increased protein, and a weakly positive spinal fluid Wassermann. Necropsy revealed no evidence of syphilitic involvement of the central nervous system, but there was an extensive meningeal leukemic infiltration. Of the 27 cases of leukemia at the Massachusetts General Hospital, 2 had lumbar punctures, 1 with normal and 1 with abnormal findings. The details of the spinal fluid examinations of the Boston cases are presented in Table 6.

Thus, 24 patients who had had lumbar punctures were collected from the 146 cases of leukemia with central nervous system involvement reported in the literature. To this number, 10 were added from 334 cases of leukemia studied at the Boston City Hospital, the Massachusetts General Hospital and the Huntington Memorial Hospital. Of this total of 34 cases available, only 9 (26.4%) had normal spinal fluids. The most frequent abnormalities of the cerebrospinal fluid were in the protein content (in 52.9% of the cases); the pressure (35.3%) and the cell content (41.4%). The changes occurring in the spinal fluid of patients with leukemia are best illustrated by the numerous observations in the case here reported, which is the first instance in which the spinal fluid was adequately studied over a prolonged period.

In all cases of leukemia neurologic examination and lumbar puncture should therefore be done. Neurologic signs and changes in the spinal fluid may at times be the only diagnostic feature of the case. Examination of the spinal fluid should include manometric pressure readings, total and differential cell count, and quantitative protein, sugar and chlorid values. If any abnormality is found, repeated

taps are indicated. Even with a normal initial fluid, lumbar punctures should be done from time to time.

Summary. 1. The clinical course of an unusual case of acute lymphatic leukemia is reported. The presenting manifestations were facial diplegia and a spinal fluid, under elevated pressure, containing 2000 cells and increased amounts of protein. The usual clinical manifestations, including the blood picture, developed later, over a period of 10 weeks. The relationship between changes in the spinal fluid and changes in the blood has been systematically studied.

2. An analysis of the literature of the past 50 years has revealed 146 cases of leukemia with neurologic signs, excluding retinal involvement. It is estimated that only about 25% of cases with histologic evidence of leukemic infiltration of the central nervous system exhibit neurologic signs.

3. An analysis of the records of 334 cases of leukemia in Boston revealed an incidence of 20.5% with neurologic signs, excluding retinal lesions. The frequency of neurologic complications in the acute and chronic types of leukemia, and in the lymphatic and myelogenous types, was about the same.

4. The most frequently observed neurologic signs were unilateral or bilateral palsies of the seventh and sixth nerves, with less frequent involvement of the fifth, eighth, ninth, tenth, eleventh and twelfth nerves. Absent deep reflexes, pyramidal signs, paresthesias and signs of meningeal irritations have also been encountered. The neurologic signs, and particularly involvement of the cranial nerves, often exhibit rapid fluctuations.

5. In 73.6% of 34 cases the spinal fluid showed abnormal findings, as indicated by increased cell count, by increased protein content, and by elevated pressure.

6. In view of the frequent involvement of the central nervous system, systematic neurologic examination of the patients and study of the spinal fluid can be of aid in the diagnosis and management of patients with leukemia.

REFERENCES.

1. Burns, A.: Observations on the Surgical Anatomy of the Head and Neck, p. 386, F. Lucas, Jr., E. J. Coale, and Cushing and Jewett, Baltimore, 1823.

2. Dock, G., and Warthin, A. S.: New Case of Chloroma with Leukemia; With a Study of Cases Reported Since 1893, Trans. Assn. Am. Phys., **19**, 64, 1904.

3. Baudouin, A., and Parturier, G.: Sur les complications nerveuses des leucémies, Rev. neurol., **19**, 673, 1910.

4. Tapie, J., and Cassar, A.: Sur deux cas de leucémie myéloide avec complications nerveuses, Arch. d. mal. du coeur, **12**, 218, 1919.

5. Fried, B. M.: Leukemia and the Central Nervous System With a Review of 30 Cases, Arch. Path. and Lab. Med., **2**, 23, 1926.

6. Trömner, E., and Wohlwill, F.: Ueber Erkrankungen des Nervensystems, insbesondere der Hirnnerven, bei Leukämie, Deutsch. Ztschr. f. Nervenh., **100**, 233, 1927.

7. Viets, H. R., and Hunter, F. T.: Lymphoblastomatous Involvement of the Nervous System, Arch. Neurol. and Psychiat., **29**, 1246, 1933.

8. Critchley, M., and Greenfield, J. G.: Spinal Symptoms in Chloroma and Leukemia, Brain, **53**, 11, 1930.

9. Diamond, I. B.: Leukemic Changes in the Brain; Report of 14 Cases, Arch. Neurol. and Psychiat., **32**, 118, 1934.

10. Hall, F. de H.: Chloroma; etc., Proc. Roy. Soc. Med., **2**, Med. Sec., 157, 1909.

11. Hill, E.: Papilledema and Intracranial Complications of Leukemia, Am. J. Ophth., **15**, 1127, 1932.

12. Barker, L. F.: Neutrophilic Myelocytes in the Cerebrospinal Fluid of a Patient Suffering from Myeloid Leukemia; etc., Southern Med. J., **14**, 437, 1921.

13. Litterer, W.: Discussion on Barker's article, Ibid, p. 441.

14. Schwab, S. I., Sale, L., and Schmidt, E. R.: Case of Myelitis Associated with the Blood Picture of Acute Leukemia, Interstate Med. J., **24**, 264, 1917.

15. Mieremet, C. W. G.: Ein klinisch unter dem Bilde eines malignen Tumors verlaufender Fall von myeloischem Chlorom. Virchow's Arch. f. path. Anat., **215**, 353, 1914.

16. Heissen, F.: Chlorom und Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat., **95**, 248, 1925.

17. Munro, E. E. H.: Acute Myeloid Leukemia Simulating Meningitis, J. Am. Med. Assn., **74**, 603, 1920.

(Owing to lack of space, the complete bibliography of the subject in not included here.)

FATAL ETHYLENE DICHLORID POISONING.

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Ethylene dichlorid, the first known of the ethylene-halogen compounds, was discovered in 1795 by Dutch chemists who named it "Dutch liquid." The formula is $CH_2Cl–CH_2Cl$. It is not to be confused with dichlorethylene $CH_2=CCl_2$ and $CHCl=CHCl$ from which it differs chemically as well as pharmacologically, especially in its action on the eye (Steindorff[1]).

Ethylene dichlorid was first used as an anesthetic (Nunneley, Simpson, Snow[2]) in 1848–1849 (Eulenberg[3]). In 1879, a committee of the British Medical Association[13] reported on the use of ethylene dichlorid as an anesthetic after experimentation on rabbits. Just when this substance ceased to attract attention as an anesthetic is not certain, but it is likely that the discovery, in 1887, by DuBois and Roux,[4] that it caused corneal opacities was a factor in its being discarded. In recent years ethylene dichlorid has found many new uses. The fourth edition of *Merck's Index*[5] listed it as an anesthetic, rubefacient and antispasmodic; it stated that it is used internally for general anesthesia, cramps and diarrhea and externally as a solvent for iodin (for skin disinfection), fats, oils, gums, resins and

esters. The maximum dose is stated as 1 cc. for single dose and 3 cc. per day.

Today ethylene dichlorid is used commercially chiefly as a solvent; in cleaning fluids and lacquers it has a wide and increasing application. It has been used to kill moths and weevils, the latter in the fumigation of grain and flour. In a mixture with carbon tetrachlorid it has been employed as a fumigant and a fabric cleaner. Sayers, Yant, Waite and Patty[6] stated that ethylene dichlorid has been cited as a stimulant for sprouting potatoes. The inhalation of ethylene dichlorid is an important problem in industrial hygiene. It is strange that in spite of its extensive commercial use, no cases of ethylene dichlorid poisoning after oral ingestion have apparently been reported previously.

Case Report. S. E., male, aged 63, accidentally drank upon an empty stomach 2 ounces of ethylene dichlorid which he has mistaken for gin and had mixed with orange juice and ginger ale. No immediate effects were felt. No alcoholic beverages were taken before or after drinking the ethylene dichlorid. Two hours later he began to feel nauseated and faint and started to vomit during the following hour. When he arrived at the hospital, 5 hours after the accident, he appeared dazed and distressed and was unable to stand. He vomited a liquid that resembled milk, which had been given to him by his family physician 3 hours before. Because the impression had been given that the fluid which he had drunk contained mercury, his stomach was lavaged with 2 quarts of milk; 8 ounces of mineral oil were left in his stomach.

On *physical examination* the blood pressure in the right arm was 152/84, in the left 136/82. The biceps, triceps and patellar reflexes were active. The skin of the body was pale, cool and dry. The face was cool and moist. The lips were slightly cyanosed. There was no jaundice. The conjunctiva was moderately injected. The extraocular movements and accommodation were normal. The pupils were dilated and equal. In bright light they constricted slightly and momentarily. The corneas were clear. The odor of the breath resembled that of chloroform but had also a pungent quality. The tongue had a heavy yellow coating. The upper pharynx was injected. Coarse râles were heard over the lung bases. The heart sounds were distant. The left radial pulse was not palpable, while the right was normal. His rectal temperature was 96.2° F., his pulse 72 and respiration 20. He continued to vomit an opaque yellowish fluid mixed with oil. He was given 750 cc. of a 10% glucose solution intravenously. A blood count taken during the night, 8 hours after the accident showed: Erythrocytes, 5,260,000; leukocytes, 11,800; 86% neutrophils (32 filamented and 54 non-filamented), 11% lymphocytes, 3% monocytes; no reticulocytes; no abnormality of erythrocytes. A urinalysis of the 16 ounces of urine voided at about this time showed: Specific gravity, 1.028; acid reaction, yellow flocculent sediment; moderate albumin; 4+ sugar; no acetone; no diacetic acid; bile salts present; bilirubin present; no urobilin; few hyalin and granular casts; no erythrocytes, no mucus, crystals or cylindroids. Seven dark brown liquid stools were passed during the night. The patient felt during this period as though he were intoxicated on alcohol except that there was no euphoria. The examination of 6 ounces of urine voided during the early morning hours showed a specific gravity of 1.009; alkalin reaction; turbid, abundant albumin, 3+ sugar; no acetone, diacetic acid, casts or erythrocytes; 5 to 7 white blood cells per high-power field; no epithelial cells, few mucous

shreds; many triple phosphate crystals; no cylindroids. He complained of a pain in his lumbar spine and later in the right lower abdomen. His rectal temperature taken during the morning hours was 99.6° F., his pulse 108 and his respiration 30. A van den Bergh test at this time showed that the direct reaction was biphasic and the indirect reaction was 4.6 units. He was drowsy and did not answer questions. Soon afterward his hands and face became cyanosed; pulse and heart sounds could not be obtained and his respiration became more labored. In spite of administration of adrenalin, atropin sulphate, caffein sodiobenzoate subcutaneously and the use of an oxygen tent the patient died 22 hours after the accident.

On *postmortem examination* (W. C. Hueper; 3 hours after death) the pleura was smooth and glistening with the exception of a few old adhesions at both apices. The lungs were well distended, grayish-red, moderately anthracotic. The lower lobes had a fleshy consistency in places and were of a darker red color. The cut surface was reddish in the upper lobes and bluish-red in the lower lobes. Dark red blood was oozing freely from the cut surface. The bronchi were free and had a velvety smooth mucosa.

The *heart* was normal for small foci of sclerosis and calcification in the wall of the coronary vessels. The aorta showed a moderate degree of sclerosis.

The *peritoneum* was smooth and glistening with no free fluid. The gall bladder, pancreas, suprarenal glands, testicles, prostate, seminal vesicles and the marrow from the femur, rib and lumbar vertebræ were normal.

The *liver* weighed 1600 gm. and measured 26 by 22 by 6.5 cm. Several deep respiratory sulci were found over the right lobe. The surface was smooth and showed a reddish-brown mottling with a few distinct yellow areas. Blood exuded freely from the cut surface which showed many irregular, small yellow areas.

The *spleen* weighed 200 gm., and measured 13 by 3.5 by 8 cm. The capsule was gray and smooth. The organ was firm and showed on the cut surface distinctly outlined follicles embedded in a dark red pulp.

The *kidneys* had moderately adherent capsules. The right organ weighed 170 gm. and measured 13 by 5 by 3.5 cm., left weighed 180 gm. and measured 13 by 6 by 4 cm. There were many small cysts and several coarser retractions present in the grayish-red cortex. The cut surface showed a reddish-gray cortex with fine red radiating stripes and well-demarcated, grayish-purple pyramids.

The *esophageal mucosa* was smooth and gray. The stomach held a large amount of a grayish-yellow, turbid liquid containing oil droplets and white floccules. The mucosa was slightly folded, swollen and grayish-red. There were no hemorrhages or ulcerations. The mucosa of the duodenum, jejunum and ileum showed a similar picture. Small red spots were present in the lower part of the mucosa of the ileum. The subserous vessels of the distended intestine were injected. The degree of hyperemia increased toward the cecum. The intestinal lumen was filled with a reddish-brown fluid. The large bowel was reddish-purple and contained a light brown, semifluid material. The mucosa of the cecum, ascending, transverse and upper part of the descending colon was markedly swollen and of deep red color.

The vessels of the *pia arachnoid* were markedly hyperemic. The *brain* weighed 1450 gm. The cut surface of the brain was hyperemic with abundant oozing of blood from the cut vessels. There was no macroscopic evidence of hemorrhages. The amount of fluid in the lateral ventricles was somewhat increased.

Microscopic Examination. The myocardium showed a moderate and diffuse infiltration with lymphocytes which sometimes formed small perivascular accumulations. The muscle cells appeared normal.

The alveoli of the lungs were distended in places and formed smaller

cavities caused by the rupture of the interalveolar septa. Alveoli located adjacent to these emphysematous regions appeared to be compressed. The vessels were filled with blood and the larger ones contained numerous leukocytes.

The bloodvessels and capillaries of the liver were distended, filled with erythrocytes and numerous leukocytes. Small hemorrhages were occasionally seen. Fatty degenerated cells were present in moderate number, especially in the periphery of the lobules.

In the *pancreas* many areas of fat tissue were found scattered in the normal parenchyma.

The *spleen* showed a marked distention of the sinuses and pulp spaces with erythrocytes. The follicles were normal.

The cortex of the kidneys showed a few arteriosclerotic scars. The tubular epithelium in the cortical region had partly lost its nuclei, a granular pinkish material filling the lumina. The lumina of the pyramids contained bluish-stained casts. Those of the papillary portions were completely necrotic in some areas, having become incrustated with calcium salts evidenced by the intensely blue staining of the cellular débris. The surrounding tubular elastic membranes, which filled in part the collapsed lumina in curl-like formations, and elastic membranes of adjacent smaller vessels were also calcified. Bluish coarse granules were seen in the cytoplasm of some tubular epithelial cells, pointing to the causative mechanism of the calcifications present in the surrounding renal tissue. The apparently well-preserved tubular epithelial cells contained on the other hand not infrequently a coarse, granular, brown pigment.

Suprarenal glands and *testicles* were normal.

Sections from the *colon* showed a complete absence of epithelial lining; only in the glandular invaginations was it well preserved. The loose connective tissue of the mucosa showed a marked imbibition of erythrocytes mixed with a moderate number of leukocytes which were mainly of the mononuclear and immature neutrophilic type. The vessels of the submucosa were engorged and contained numerous leukocytes. There was a diffuse erythrocytic infiltration in the submucosa. A marked vacuolar and granular degeneration with a loss of the normal longitudinal striation and cell structure was present in the muscularis. Sections from the ileum revealed a marked leukocytic infiltration of the mucosa and extensive granular degeneration of the muscularis. The submucosa was hyperemic and edematous. The cells of the nervous plexus in the ileum and colon seemed to be normal.

Sections prepared from the *basal ganglia of the brain* showed many small perivascular hemorrhages. The bloodvessels were hyperemic and there was a moderate increase in the number of small glia cells around some of the smaller vessels. The cerebellum was normal.

The *skeletal muscle* removed from the abdominal wall contained an interstitial, lymphocytic infiltration which was diffuse and marked. A small, ovoid cyst filled by the sectioned parts of a trichina was found in the interstitial tissue, where it was surrounded by a dense lymphocytic accumulation.

The *femur* contained normal fat marrow throughout in which were scattered a few small foci of myeloid tissue. A rib and two vertebræ contained normal myeloid marrow except that a slight increase of nucleated erythrocytes seemed to exist.

PATHOLOGICAL DIAGNOSIS: Hemorrhagic colitis; nephrosis with calcifications of the tubular epithelium and tubular and vascular elastic membranes; fatty degeneration and passive congestion of the liver, passive congestion of the spleen and lungs; multiple perivascular hemorrhages of the brain; chronic myocarditis and myositis due to trichinosis.

Comment. The toxic action of ethylene dichlorid was already reported on by the early investigators of this substance.[18] Eulenberg, in 1876, anesthetized rabbits with it and found that it caused dizziness, mydriasis, complete insensibility of the cornea and hyperemia of the conjunctiva. The committee of the British Medical Association[13] noted convulsive movements that persisted until death in the rabbits anesthetized with ethylene dichlorid (1879). DuBois and Roux,[4] in 1887, DuBois,[7] in 1888, Parnas,[8] in 1888, Faravelli,[14] in 1892, Erdmann,[17] in 1912, Bullot,[9] in 1896, and Steindorff,[1] in 1922, observed during the course of extensive experimentation with ethylene dichlorid that this substance, when inhaled or injected subcutaneously or intravenously, caused a temporary, white, blue-white opacity of the cornea in various animals. These opacities, they found, cleared up from the periphery after several months and were due to an infiltration of the cornea by lymphocytes and connective tissue cells. It may be mentioned in this connection that ethylene dichlorid is the only saturated chlorin compound of the ethane series that has this action. Among the unsaturated compounds that have a similar effect in dichlorethylene. The acute effect of ethylene dichlorid on the eye is a maximal dilatation of the pupil which may change after some time to myosis and anisocoria. Joachimoglu[15] found that ethylene dichlorid has about the same anesthetizing effect as chloroform, but that its hemolytic action is only half as strong as that of the latter substance. Kiessling[16] studied the action of this and related halogen compounds on the isolated frog's heart.

Kistler and Luckhardt,[10] who recently investigated the pharmacologic action of this substance, introduced into dogs ethylene dichlorid either by stomach tube or by intravenous injection. In general, dogs that did not die of the immediate effects (drop in blood pressure, excitement, incoördination, salivation followed by drowsiness, vomiting and dyspnea) of the drug passed through a stage characterized by depression, general sickness, emaciation, anorexia, lack of thirst, dyspnea, tarry stools and corneal opacities lasting several weeks, before they gradually recovered. The postmortem findings typical of all dogs that died from the effect of the poisoning were as follows: Delay of *rigor mortis* by several hours, bloody discharge from mouth and nostrils, edema of the lung, subserous hemorrhages of the heart, hyperemia of the liver, brownish discolorization of the liquid blood, hemorrhages into the mesentery and intestinal lumen, albumin and bile pigments in the urine.

Sayres, Yant, Waite and Patty,[6] who exposed guinea pigs to the vapors of ethylene dichlorid, noted similar symptoms and postmortem findings (irritation of eye and nose, vertigo, static and motor ataxia, retching movements, unconsciousness, incoördination

of extremities, first increased and later slowed and shallow respiration with low concentration and rapid and jerky breathing of dyspneic type with higher concentrations).

Ploetz[11] stated that ethylene dichlorid had a hemolytic effect and Plagge[12] noted that this substance inhibited fermentation of yeast.

Many of the clinical and pathologic manifestations seen in the experimental animals were paralleled in this case. The outstanding symptomatic similarities were mydriasis, dizziness, increasing stupor and the gradually progressive circulatory failure which was manifested by cyanosis, rapid pulse and unsatisfactory response to glucose, adrenalin, oxygen and atropin.

The appearance of large amounts of albumin and sugar in the urine and the occurrence of extensive tubular necrosis with calcifications resembling those seen in mercury dichlorid poisoning indicated that the kidney is the excretory organ of this substance or its decomposition product which is presumably oxalic acid. The hemorrhagic condition of the mucosa of the colon, on the other hand, was most likely the result of the toxic action of ethylene dichlorid exerted upon the intestinal mucosa during the process of absorption. It can be justly assumed that under the conditions present in this case the ingested liquid reached this part of the alimentary tract without any great delay and left for these reasons no marked injurious effects upon the upper portions of the digestive system. This observation may possibly be of some value in the future therapeutic management of cases of this type, because it suggests that high colonic irrigations given early enough and in sufficient amounts may help to remove mechanically the ingested toxic material before it can be absorbed and cause irreparable organic damage. The histologic changes existing in the brain accounted to a certain extent for the nervous symptoms observed.

In the absence of any marked myocardial lesion the actual direct cause of death was apparently a "hemorrhage" into the dilated capillary system of the internal organs resulting in circulatory failure.

Summary. Ethylene dichlorid, known since 1795 and first used as an anesthetic, has recently come into widespread, commercial use as a solvent and cleaning fluid.

A patient who drank 2 ounces of this liquid died within 22 hours. Stupor, vomiting, diarrhea, cyanosis and subnormal temperature were the outstanding clinical symptoms. Death was apparently caused by circulatory failure.

The ingested substance caused an extensive hemorrhagic colitis, nephrosis with marked tubular calcifications and a generalized passive congestion of the internal organs beside multiple perivascular hemorrhages in the region of the cerebral basal ganglions.

BIBLIOGRAPHY.

1. Steindorff, K.: Ueber die Wirkung einiger Chlorderivate des Methans, Aethans und Aethylens auf die Hornhaut des Tierauges, Arch. f. Ophthal., **109**, 252, 1922.
2. Nunneley, T., Simpson, N., and Snow: New Anesthetics, Providence Med. and Surg. J., p. 98, 1849; Chlorid of Olefiant Gas as an Anesthetic, Ibid., p. 138; Anesthetic Effects of the Chlorid of Olefiant Gas, Ibid., p. 166.
3. Eulenberg, H.: Handbuch der Gewerbehygiene, Berlin, p. 401, 1876.
4. DuBois, R., and Roux, L.: Action du chlorure d'éthylène sur la cornée, Compt. rend. de l'Acad. des sci., **104**, 1869, 1887.
5. Merck's Index, 4th ed., American Series, Rahway, N. J., Merck & Co., Inc., p. 226, 1930.
6. Sayers, R. R., Yant, W. P., Waite, C. P., and Patty, F. A.: Acute Response of Guinea Pigs to Vapors of Some New Commercial Organic Compounds: Ethylene Dichlorid, Pub. Health Rep., **45**, 225, 1930.
7. DuBois, R.: Action physiologique du chlorure d'éthylène sur la cornée, Compt. rend. de l'Acad. des sci., **107**, 482, 1888.
8. Parnas, M.: Action des inhalations du chlorure d'éthylène pur sur l'oeil, Ibid., p. 921.
9. Bullot: Demonstration of a Case, Meeting, December 20, 1896, Soc. Bàlge d'ophth., Zentralbl. f. prakt. Augenheilk., **21**, 124, 1897.
10. Kistler, G. H., and Luckhardt, A. B.: Pharmacology of Some Ethylene Halogen Compounds, Current Res. in Anesth. and Analg., **8**, 65, 1929.
11. Ploetz, W.: Vergleichende Untersuchungen über die haemolytische Wirkung einiger Chlorderivate des Methans, Aethans und Aethylens, Biochem Ztschr., **103**, 242, 1920.
12. Plagge, H.: Vergleichende Untersuchung über die gaerungshemmende Wirkung einiger Chlorderivate des Methans, Aethans und Aethylens, Ibid., **118**, 129, 1921.
13. Lyman, H. M.: Artificial Anesthesia and Anesthetics, New York, William Wood & Company, p. 205, 1881.
14. Faravelli, E. A.: A proposito dell'azione delle inhalazioni di bicloruro di etilene sulla cornea, Arch. per le scienze med., **16**, 79, 1892.
15. Joachimoglu, G.: Die Pharmakologie des Trichloraethylens (Chlorylen Kahlbaum), Berl. klin. Wchnschr., **58**, 147, 1921.
16. Kiessling, W.: Vergleichende Untersuchungen über die Wirkung einiger Chlorderivate des Methans, Aethans und Aethylens am isolierten Froschehrzen, Biochem. Ztschr., **114**, 292, 1921.
17. Erdmann: Ueber Augenveraenderungen durch Aethylenchlorid, Klin. Monatsbl. f. Augenheilk., **50**, N.F. 14, 370, 1912.
18. Luckhardt, A. B., and Lewis, D.: Clinical Experiences with Ethylene Oxygen Anesthesia, J. Am. Med. Assn., **81**, 1851, 1923.

SPINDLE CELL SARCOMA OF THE PANCREAS.

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Sarcoma of the pancreas is very rare. Gruber could not find one sarcoma among 20,302 autopsies. In the older literature there is a report by Remo Segré who mentions among 11,492 postmortem

examinations 132 neoplasmata of the pancreas, 2 of them classified as sarcomata.

Although the number of sarcomata of the pancreas given in the literature is very small, the larger part of them cannot stand criticism and should not be quoted as sarcomata.

Three different types are described: Round cell, giant cell, and spindle cell sarcoma. Marxer, analyzing these three forms in a thorough and lucid study, found that the small number of sarcomata of the pancreas should be reduced still further. He was able to prove that many of the reported pancreas sarcomata are either lymphosarcomata or metastatic tumors or not true blastomata at all, but of inflammatory origin. Some of the old cases could not be considered because they have no microscopic findings.

Among the so-called round cell sarcomata he finds lymphosarcomata, aleukemic leukemia and lymphogranuloma. It is interesting that the case of Litten which is quoted in so many papers as the first described sarcoma of the pancreas is really a lymphosarcoma. In Halasz' case Marxer is able to rule out pancreatic sarcoma, pointing out the diffuse infiltration of the mesenteric and periportal lymph nodes, and two nodular tumors in the hilus of the lung and in the mediastinum.

No blood findings are given. The diffuse infiltration speaks decidedly for a generalized lymphosarcomatosis. In fact, Marxer concludes that the existence of round cell sarcoma of the pancreas has still to be proved. The same is true of the giant cell sarcoma. The giant cell sarcoma described by Weil is apparently a lymphogranuloma and not a sarcoma.

Thus the spindle cell sarcoma is the only type that can stand criticism. Following is a short review of the cases of spindle cell sarcoma of the pancreas.

Briggs first described spindle cell sarcoma of the pancreas (1890) and Neve next (1891). Schuele first called attention in his report of a spindle cell sarcoma to the pseudocystic structure of his tumor.

In 1901 Boyd described a cystic spindle cell sarcoma with profound cachexia but no metastasis. Malcolm (1902) found a fibrosarcoma of the pancreas in a child 4 years old.

In the same year Oleari published a case with thrombosis of the portal vein and infiltration of the parenchyma of the liver.

In 1903 Ehrlich described 2 tumors of the pancreas, one an endothelioma and the other a spindle cell sarcoma weighing 3000 grams. Both were cystic. Sobolew's 4 cases (1910) illustrate the difficulty of distinguishing between primary and secondary growths of the pancreas. Two of his cases are definitely metastatic, 1 arising from a myosarcoma of the uterus. One is probably metastatic and the last is a true spindle cell sarcoma of the pancreas.

In 1912 Costantini described a primary spindle cell sarcoma of

the tail and body of the pancreas. Metastases in the liver were present.

In 1921 Lockwood described a spindle cell sarcoma of the pancreas and in 1925 Marxer a unilocular cyst with nodular wall and intensely thickened base, which microscopically proved to be a spindle cell sarcoma.

In 1930 Tscherpnina described a pleomorphic sarcoma of the pancreas head combined with an intense sclerosis of the body and the tail and with cirrhosis of the liver.

In this report a case of spindle cell sarcoma of the pancreas will be described.

Case Report. The patient (studied clinically by Dr. R. W. Blumenthal) was a male, aged 57, married, and by occupation a butcher. His wife and 1 child were living and well, 1 child dying at the age of 10. There were no miscarriages. His father is in good health, aged 84, while his mother died of cardiac disease at 78. Three brothers and 1 sister are living and well. There is no other history of heart, or kidney disease, diabetes, cancer, or insanity in the family.

He was admitted to the hospital for the first time in March, 1932, after several years of slowly progressing weakness. Six months previously he had had a severe chill followed by fever and vomiting which recurred at irregular intervals over the next 3 months and was associated with moderate loss of weight. During the next 3 months he felt relatively well, however, gained 30 pounds and was able to return to light work. Immediately preceding his admission to the hospital he had again had fever, chills and vomiting.

Physical examination at the time revealed a patient who did not appear to be in acute pain. His remaining teeth were in poor condition. The eyes reacted normally; the lungs were apparently normal. The heart was slightly enlarged with a soft mitral murmur. The pulse was small and slow, the vessels were beaded.

The rounded abdomen showed a small umbilical hernia, no masses or tender areas. The liver border was 1 cm. below the costal margin. The spleen was not palpable. Reflexes, rectal and prostate examinations were negative.

Laboratory findings: Basal metabolic rate plus 20%; blood Wassermann, Kahn and Widal tests negative; blood culture, no growth; blood sugar, 196 mg. per 100 cc. of blood, non-protein nitrogen 38.7 mg. per 100 cc. of blood; creatinin 1.2 mg. per 100 cc. of blood; blood in feces, benzidine test for positive, guaiac and Rolland tests negative; electrocardiogram showed slight evidence of coronary sclerosis; red blood count 5,650,000; white blood count 18,300. On the patient's second admission (May 12) urobilinogen was found in the urine (diluted 1 to 8). Five days later it was negative; then became positive again—after 3 days (immediately after operation) it was 1 to 2. From this time on the urobilinogen increased gradually—May 24, 1 to 3; 25th, 1 to 30; 26th, 1 to 75; 27th and 28th, 1 to 50; 31st, 1 to 80; June 1st, 1 to 100. Then it came down to 1 to 40 until he died June 4th. There was always bile pigment in the urine.

His highest temperature while in the hospital was 104° F., the highest pulse rate 108, respiration 22. The urinary sugar ranged from 4+ to negative. He was discharged from the hospital April 18, 1932, as improved, with a probable diagnosis of subacute bacterial endocarditis and diabetes mellitus.

After a few days at home he was forced to go to bed on account of fever

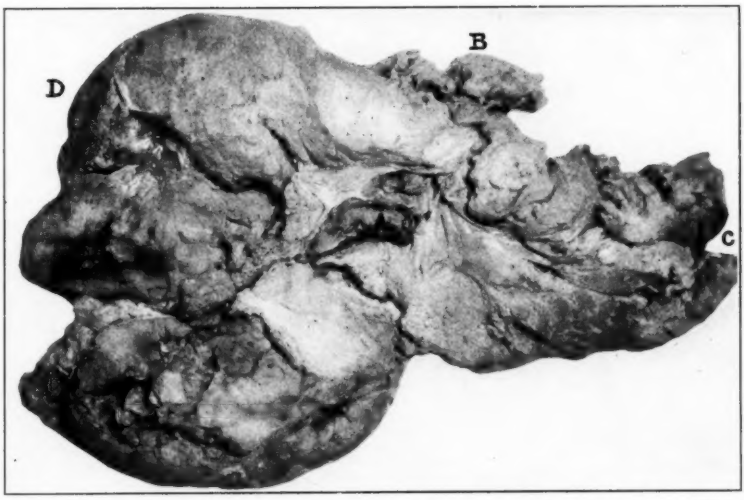

FIG. 1.—Gross view of incised pancreas. *A*, Thrombus; *B*, body; *C*, tail; *D*, head.

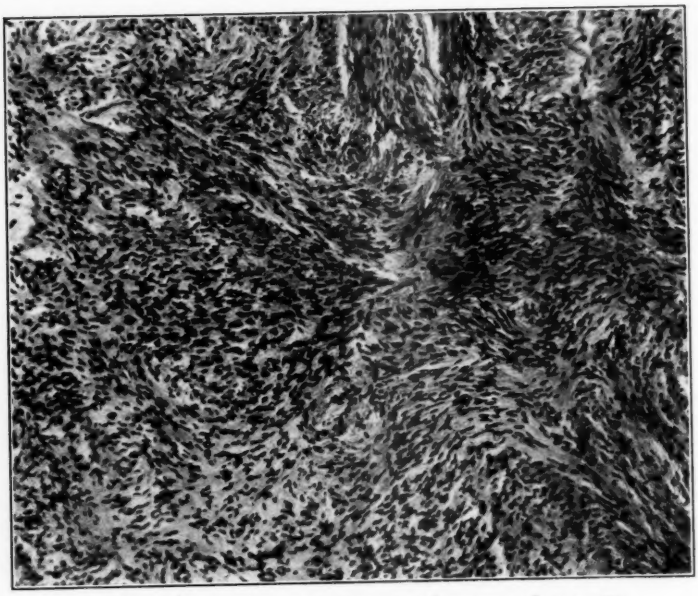

FIG. 2.—Microscopic section: sarcoma of pancreas, low power.

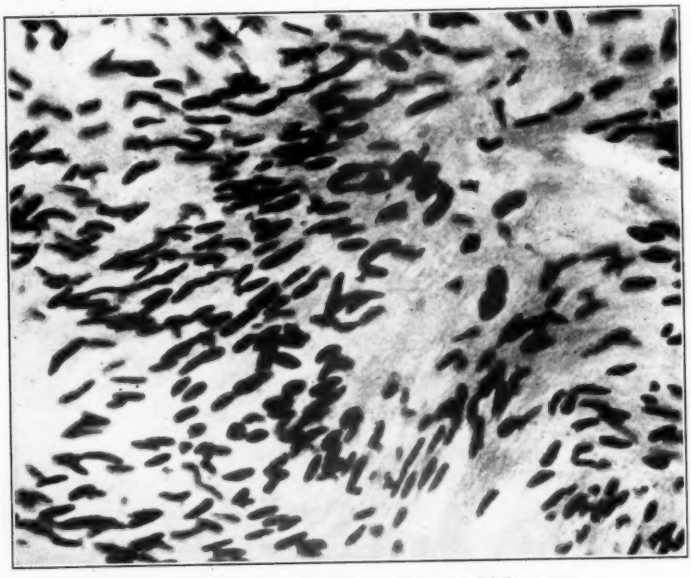

FIG. 3.—Microscopic section: the same high power.

and weakness. He had had no pains or chills. Usually he felt well in the morning but by evening the fever and sweating would begin. There had been considerable loss of weight as well as a moderate jaundice.

He entered the hospital a second time on May 12, when his blood pressure was 110 systolic and 64 diastolic, his nutrition poor, and he was apparently very sick. The history of jaundice, anorexia, loss of weight, with physical findings of tenderness in the gall bladder region, together with a mass in the right subcostal area, suggested cholecystitis with adjacent pancreatitis (possibly malignant) and hepatitis. A Roentgen ray examination of the gall bladder with dye revealed a normally functioning gall bladder, which was pushed laterally and deformed by a tumor in the midabdomen. The entire duodenum was displaced laterally in half a circle, probably by tumor originating in the pancreas.

An *exploratory operation* (May 20) revealed an enormously distended, thin-walled gall bladder, as with a carcinoma of the pancreas or a stone in the ampulla. The pancreas was the size of two fists but not nodular. The liver was large with rounded edges and irregular areas. After the exploratory operation he ran a stormy course and died June 5, 1932.

Postmortem Examination (by Dr. E. J. Oesterlin 3 hours after death):

Anatomic Diagnosis. Pleomorphic spindle cell sarcoma of the pancreas.

The head of the *pancreas* was enlarged to the size of a large grapefruit and contained many cystic cavities, without apparent epithelial lining. The entire parenchyma of the pancreas was replaced by a coarse fibrous tissue. Microscopically, the tissue consisted partly of mature coarse connective tissue fibers and partly of irregular whorls of pleomorphic cells, among which spindle shaped cells predominated. Occasional giant cells were found. Scattered through the tumor were necrotic areas, invaded by neutrophils. The margins of the cystlike spaces was also invaded by neutrophils. The body and tail of the pancreas showed marked fibrosis.

The *spleen* was much enlarged, weighing 370 gm. The pulp was easily scraped from the cut surface.

Acute splenitis.

The *liver* was considerably enlarged, weighing 2130 gm. It contains multiple abscesses, frequently fused, varying in size up to 4 cm. in diameter. Culture of the pus showed B. coli.

Microscopic examination showed many necrotic areas invaded by neutrophils, with adjacent granulation tissue. There were also chronic changes present: the periportal connective tissue and the bile ducts were much increased. The liver cells showed fatty degeneration.

Multiple abscesses in cirrhotic liver.

Thus there were parallel acute and chronic processes in both the pancreas and liver. The acute process consists in the inflammatory cyst formation of the pancreas and in the liver abscesses; the chronic process in the fibrosis of the pancreas and the cirrhosis of the liver.

It seems probable that the sarcoma of the head of the pancreas was developed on a preëxisting fibrosis. The fact that there was still much mature connective tissue remaining in the head of the pancreas points distinctly in this direction.

Boyd, Constantini and Tscherpnina also report fibrosis of the pancreas in their cases.

Summary. 1. A spindle cell sarcoma in the head of the pancreas has been described.

2. The sarcoma was combined with a marked fibrosis of the body

and tail of the pancreas and with cirrhosis of the liver with multiple abscesses.

3. The possibility of a causative relation between the fibrosis of the pancreas and the sarcoma has been stressed.

4. A review of the definite spindle cell sarcomata in the literature is given.

BIBLIOGRAPHY.

Boyd, G. A.: Sarcoma of the Pancreas, J. Am. Med. Assn., **36**, 1461, 1901.

Briggs, W.: Tumor of the Pancreas, St. Louis Med. J., **58**, 154, 1890.

Constantini, G.: Sarcoma primitivo del pancreas, Tumori, **1**, 735, 1912.

Crooks, J.: Secondary Sarcoma of the Pancreas Causing Jaundice in Child, Lancet, **1**, 973, 1925.

Ehrlich, C.: Ein Beitrag zur Causuistik der Pancreasgeschwuelste, Münch. Med. Wchnschr., **1**, 368, 1903.

Ehrmann, F.: Primary Sarcoma of the Tail of the Pancreas, J. Am. Med. Assn., **27**, 1240, 1896.

Halasz, A.: Primaeres Sarcom der Bauchspeicheldruese, Wien. klin. Wchnschr., **21**, 1807, 1908.

Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, **2**, 537, 1929, Julius Springer, Berlin.

L'Huiller, A: Congenitales Lymphosarkom des Pancreas, Virch. Arch., **176**, 507, 1904.

Litten, M: Ein Fall von Pancreas Sarcom mit enormen Metastasen bei einem 4 jaehr. Knaben, Deutsch. Med. Wchnschr., **14**, 901, 1888.

Lockwood, C.: Tumors of the Pancreas, J. Am. Med. Assn., **77**, 1554, 1921.

Malcolm, J. D.: Removal of a Sarcomatous Tumor from the Tail of the Pancreas of a Child 4 Years and 8 Months Old, Lancet **1**, 586, 1902.

Martin, M.: Zur Chirugie der Pancreascysten, Deutsch. Ztschr. f. Chir., **100**, 306, 1909.

Marxer, H.: Ueber das Pancreas sarkom. Arch. f. klin. Chir., **135**, 606, 1925.

Neve, E. T.: The Morbid Anatomy of the Pancreas, Lancet, **2**, 659, 1891.

Oleari, A.: Sopra un caso di tumore primitivo della testa del pancreas, La clin. Chir., **10**, 1037, 1902.

Rijssel, E. C. van: Reuscellen sarcom van de schildklier en het pancreas, Tijdschrift voor Genesskl., **55**, 201, 1919.

Schirokogorff, J.: Primaeres Sarkom des Pancreas, Virch. Arch., **193**, 395, 1908.

Schueler, F. A.: Ein Fall von Sarcoma pancreaticum hemorrhagicum, Med. Inaug. Dissert. Greifswald, 1899. Quoted after Henke und Lubarsch.

Sobolew, L. W.: Beiträge zur Pancreaspathologie, Ziegler's Beitr., **47**, 300, 1910.

Tscherpnina, M. I.: Ein Fall von primaeren Pancreas Sarkom, Cbl. f. allg. and path. Anat., **50**, 50, 1930.

Weil, E.: Primaeres Riesenzellensarcom des Pancreas, Prager Med. Wchnschr., **30**, 563, 1905.

CONGENITAL CYSTS OF THE LUNG.*

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In 1925 Koontz[1] collected and examined 108 cases of congenital cysts of the lung, of which 43 were in children, and, as he notes,

* Read before the Philadelphia Pediatric Society, June 14, 1932.

none reported in American articles. Further perusal of the literature adds a rather limited number of cases, some of which appear in American journals. In view of the paucity of articles upon this subject, and in view of the rapidly expansile nature of the lesions observed, the authors feel that the following case merits reporting.

Case Abstract. C. W., aged 4 months, colored, was admitted to the Children's Hospital of Philadelphia, November 9, 1931. His father was 45 years old and was said to be well. His mother was 39 years old, said she was well, and had had no miscarriages, but had given birth to 11 children, of whom 10 were living. One boy had died at 1 year of pneumonia. There was no history of syphilis or tuberculosis in the family.

The patient was born by a normal delivery at full term and weighed 9 pounds. His newborn period was without symptom or difficulty. He was breast fed for 3 weeks and then fed upon a suitable and adequate cow's milk formula, upon which he developed well. He was given orange juice and cod-liver oil in proper amounts.

The child's illness began 2 weeks before admission with coryza and cough. He did not seem very ill until 1 week had passed, when he developed a high fever, cough and rapid, grunting respiration. His sleep was disturbed, but he took his formula well. He vomited a little with his cough, and had 6 to 8 green, watery stools a day. There were no convulsions.

At the time of admission the physical examination showed the following: A well developed child, breathing regularly but rapidly, restless, and with some retraction of the head. The skin was dehydrated. The fontanelle was small and full. No craniotabes was present. The left ear drum was red and full; there was some mucous secretion in the nares. The lips were dry and the tongue somewhat coated. No teeth were erupted. The tonsils were normal in size but were reddened, as was the postpharyngeal wall. The eyes were normal. There were no enlarged glands present. The chest was of normal girth and contour and showed slight beading of the ribs. There was dullness over the left upper lobe with bronchial breathing and many crackling râles in the left axilla. The liver was palpable in the normal position for the age. The epiphyses were slightly enlarged. The reflexes were normal.

A diagnosis of left upper lobar pneumonia was made. Immediate steps were taken to combat the dehydration and prostration. A transfusion of 50 cc. of citrated blood was given, followed the next day by a hypodermoclysis of 150 cc. of saline. After several days, signs of consolidation were noted in the right upper lobe. A diagnosis of migratory pneumonia was made, and another transfusion of 35 cc. was given. After about 3 weeks the temperature descended rather gradually into a normal zone, where it stayed for 3 weeks more. During the first 3 weeks otitis media was present and both ears were opened upon a number of occasions. During the period of acute illness, the child at first gained weight; but later, due to anorexia and vomiting, this gain was lost. After the temperature became normal, the child began to gain again. In spite of this normal temperature and gain of weight, there was no appreciable clinical improvement so far as lung findings were concerned. About 6 weeks after admission the temperature began to rise again, but during this rise the child seemed to be making a gain of strength, and even gained some weight. However, after about 2 weeks of fever, attacks of weakness and cyanosis came on, and in one of these attacks, on January 18, 1932, the infant died.

Laboratory Findings. Urines were normal save for traces of albumin; the Wassermann and Kahn tests and blood culture were negative. Mantoux tests with ascending doses of old tuberculin were all negative. The blood

at the time of admission showed a secondary anemia, 39% hemoglobin, 2,150,000 erythrocytes, 12,500 leukocytes, 91% of which were neutrophils. After treatment with transfusions and iron medication, in 1 month this rose to 70% hemoglobin and 3,920,000 erythrocytes. This latter figure was not due to anhydremia.

At first, our impression was that of a migratory type of lobar pneumonia with delay of resolution, due perhaps to the severity of the secondary anemia. A further thought was that the delay was due to an underlying tuberculous infection. The negative family history, the persistently negative tuberculin reaction, the absence of tubercle bacilli in the gastric contents, made it impossible to confirm this diagnosis, yet its possibility was not entirely excluded. Still later a diagnosis of abscess of the lung was considered, and this likewise could neither be confirmed nor rejected positively.

Roentgenologic Findings. The findings made by Dr. R. S. Bromer in a series of films, a number of which are reproduced here, may be summarized as follows:

At the time of admission, films showed a bilateral consolidation. It was suspected that the lesions were tuberculous and that fluid was present between the upper and lower lobes of the left lung. A week later (Fig. 1) the right upper lobe was much clearer and the appearances suggestive of cavity were gone. It was believed that these had been caused by an emphysematous bleb. The left upper lobe was denser than before, and a ringlike shadow had appeared below it. This was also believed to be due to an emphysematous bleb. Two weeks after admission the left upper lobe was less dense, but two ringlike shadows were seen.

Five weeks after admission a film showed at the left base a large, round, ringlike shadow, also a number of smaller ones in the left upper lobe. Six weeks after admission films showed a return of the density in left upper lobe and showed the ringlike shadow still present. Seven weeks after admission the large ring shadow was thought to resemble an abscess cavity or possibly a pneumothorax.

Eight weeks after admission multiple large, circular shadows were found in the left upper lobe; the ring shadow in left lower lobe had decreased in size. It was thought that because they were so large that they could not be due to emphysematous blebs, but might be due to abscess cavities. It was argued, however, that if they were abscess cavities, they should not almost disappear at times, and should not decrease in size.

The last film was taken 4 days before death. It showed all the cavities previously mentioned, and one in the right upper lobe. The large ring-shaped shadow in the left lower lobe was shown to displace the lower branch of the left bronchus, and for this reason pneumothorax was considered the most likely cause.

Necropsy (by Dr. Waltz, 2 hours after death). *Gross Description. Left Lung.* The upper lobe is deeply grooved across the lower anterior portion, producing almost complete separation into a middle and upper lobe.

The upper outer and posterior portion of the upper lobe is attached to the chest wall by firm, fibrous adhesions. On breaking these adhesions a large, thin-walled cavity was ruptured with an outward gush of air. This cavity occupies most of the upper lobe, is empty, and measures 4.5 by 4.5 by 4 cm. The lining is smooth, but the wall is ribbed and grooved by what appears as an interlacing of dilated or thickened bronchi. The cavity shows direct connection to one of the larger bronchi. A probe being easily passed through the bronchus along one side of the cyst wall

FIG. 1.—November 19, 1931. Increased density in left upper lobe with a small kidney-shaped rarefaction. A ring shadow in the upper lobe and a smaller ring shadow on the interlobar line (1.5 x 2 cm.).

FIG. 2.—December 17, 1931. Shows lessening of density in lungs, especially over the cyst in the left upper lobe; the lower ring shadow is much larger (2.5 x 3.5 cm.).

FIG. 3.—January 9, 1932. Lower ring shadow much larger (3.5 x 4.5 cm.). Upper shadow larger and has a loculated appearance. Pneumonia cleared up.

FIG. 4.—January 14, 1932 (4 days before death) oblique. Shows further increase in size of interlobar ring shadow. The cavity in the upper lobe has increased enormously. Taken at the time dyspneic attacks began.

FIG. 5.—Bronchi up, left lung to right; below, large cyst in interlobar space. Upper lobe cysts under white roughened area. Right lung to left. Incision into cyst in upper lobe, walls of which are separated by a stick.

FIG. 6.—Left lung. Cysts of upper lobe and interlobar space laid open.

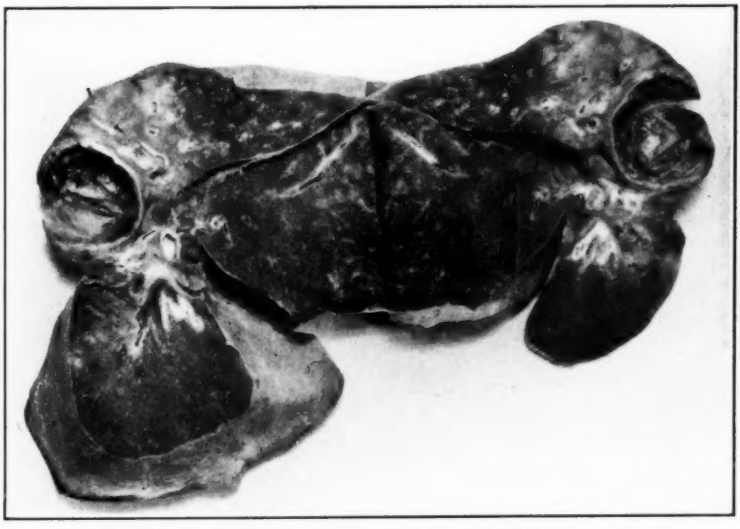

FIG. 7.—Right lung. Cyst of upper lobe laid open.

Low power (100 ×).

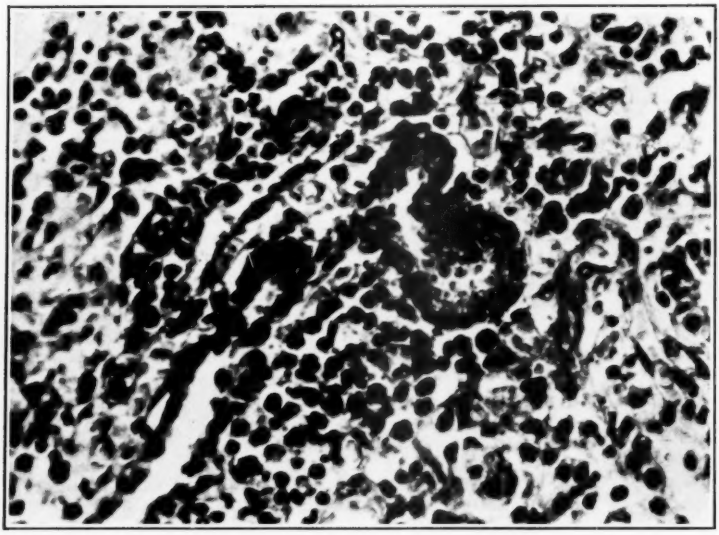

FIG. 8.—(High power 440 ×.) Adenomatous or acinus-like spaces somewhat resembling rudimentary bronchi, with flattened atypical epithelium. The blood-vessels show thickened walls. The alveoli are partially collapsed and infiltrated with small round cells; the walls are thickened with fibrous connective tissue.

for 2 cm. before opening into the cyst. Pressure on the side wall from air within the cyst could easily produce a valve effect by compressing the bronchus during expiration. A small lower posterior tip of the lobe is consolidated. The upper anterior portion of the lobe shows several small cystlike cavities ranging from a few mm. to 1 cm. in diameter. These are smooth walled, some contain pus. Between these cysts the lung tissue is firm and fibrous.

The extra middle lobe is fairly crepitant throughout. There are no cysts demonstrable in this lobe.

The lower lobe is deep red in color and boggy. There are no cysts found within the lobe. However, there is a large, thin walled cyst bulging out in the interlobar fissure between the lower and middle lobe. The cyst cavity is 4 by 4 by 4 cm. and contains only air. The lower portion of the wall is apparently part of the interlobar pleura of the lower lobe. The upper portion is part of the interlobar pleura of the middle lobe, the anterior and posterior walls are apparently a continuation of these pleural coverings, and are bluish and almost transparent. This cavity was thoroughly studied for a possible opening from a bronchus, but none could be demonstrated.

Right Lung. The lung consists of the normal three lobes. There are firm, fibrous adhesions over a small area of the posterior part of the upper lobe; when these are freed a small air-containing cyst 1.5 cm. in diameter is elevated above the surface somewhat, but extends into the lung for the most part. Near this are two other slightly elevated areas which are about 1 cm. in diameter which, on section, appear to be made up of small honeycomblike air-containing cysts. Below these is a larger cyst 3.5 by 3.5 by 3 cm., situated in the lower part of the upper lobe posteriorly, so that the wall on the lower surface is the interlobar pleura of the upper lobe. The cyst is smooth walled, but filled with thick, creamy pus.

The middle lobe is fairly crepitant throughout. The lower lobe is of a deep red color and boggy, apparently congested and edematous; no cysts are demonstrable in this lobe.

All cysts containing pus or fluid were cultured and examined for tubercle bacilli and parasites. Cultures showed Group IV pneumococcus in all such cysts. In some cysts Bacillus coli was also present. No tubercle bacilli or parasites were found in any cyst.

Microscopic Findings. The large interlobar cyst of the right lung is covered with a thin wall of fibrous connective tissue. On part of the wall no lining epithelium can be demonstrated; in other areas it is covered with a single layer of low epithelium with fairly large nuclei; in a few places these are arranged in layers of two or three cells. The nuclei are elliptical with the long axis parallel to the cyst wall. These cells do not have the appearance of the usual columnar epithelium of the bronchi, differing in the absence of cilia, in form, and in the direction of their nuclei. They have more the appearance of a type of squamous epithelium. It suggests that they had been subjected to the stretching of the cyst wall and to the long continued pressure from the cyst contents. Subjacent to the cyst wall the alveolar tissue is partially atelectatic.

The largest cyst in the upper right lobe shows a lining similar to that just described. In the partially consolidated and partially atelectatic tissue subjacent to this cyst are found rather well developed bronchi surrounded by partially collapsed alveoli somewhat infiltrated with small round cells; the alveolar walls are markedly thickened with fibrous connective tissue. These areas show many small bloodvessels with thickened walls. Grouped about a bronchus are frequently found acinus-like spaces lined with somewhat flattened ciliated columnar epithelium.

This picture suggests a hyperplastic growth of bronchial tissue corresponding to that of Stoerk,[2] which he considered a tumor of embryonal

bronchial tissue. Couvelaire[3] also described a cystadenomatous formation in his case. The cyst in the left upper lobe is filled with pus and is largely denuded of epithelium. Surrounding this cyst is a rather thick area of fairly firm, fibrous connective tissue showing loops of new bloodvessel formation.

Comments. According to Eloesser,[4] congenital cysts may be divided into two principal classes: 1, Large solitary cysts; 2, multiple smaller cysts. The latter condition is usually spoken of as congenital cystic disease; the cysts may be few and fairly large, or they may be small and too numerous to count. In the latter circumstance, they receive the designation of "honeycomb lung."

Solitary cysts vary greatly in size. They may be large enough to occupy the space usually occupied by a whole lobe of a lung. They may be of a size which can be concealed within the lung parenchyma. Sometimes they are mere outpouchings from the trachea, esophagus, or a bronchus. They have been known to be large enough to pass through the diaphragm into the abdominal cavity.

Cystic disease, or honeycomb lung, is disposed in different ways in different cases. At times a whole lobe is diffusely involved. At times a whole lung is involved. At times only part of a lobe is affected. At times, as in this case, cysts may be found in widely separated parts of both lungs.

The cysts may communicate directly with a bronchus, but in many cases this communication is not present and the cyst cavity is isolated. In some instances the cysts appear to be dilatations of a main bronchus, and branch bronchi or secondary cysts may be found opening into them. More frequently they seem to be dilatations of small bronchioles, either communicating or non-communicating. At times a number of these closed sacculations appear to be strung upon a fibrous cord, like beads upon a thread.

Cysts are usually lined with a single layer of ciliated columnar epithelium. The cyst walls are usually smooth, usually free of ulceration and inflammatory deposits, indicating that they are not broken down abscess cavities. The lining wall, however, may become inflamed. They usually contain air, or fluid, or more often both together. The fluid is said to be very high in albumin content, and, in a number of cases, of a brownish color. It usually contains few cells, if inflammation is absent. Anspach and Wolman[5] suggest that the cysts originally are fluid filled and that later this fluid is extruded by coughing or other pressure, as happened in a case described by them.

In cases where the ciliated epithelium is not present, we find a lining of one or more layers of cuboidal or even flattened epithelium. There may be no lining at all, the fibrous membrana propria forming the cyst wall. External to this are frequently found concentric fibers of smooth muscle, and at times pieces of cartilage. The amount of muscle fiber and cartilage is usually too great to suggest

that it is a mere expansion of that normally present in a bronchus. It is more probably due to an actual hyperplasia. In some cases mucous glands are found in the cyst wall. In addition to inflammation of the lining wall of the cyst, inflammation of the tissues immediately surrounding the cyst is frequently found. This is usually pneumonic in type.

Clinical Considerations. Cases arrange themselves clinically into two main types. The first type has been termed *infantile* and is characterized by sudden attacks of dyspnea, cyanosis and collapse, in which death may occur. The other type is spoken of as the chronic form. In this form, bronchopneumonic areas are found in the cystic lung. In the case reported, both dyspneic attacks and bronchopneumonia were found. In many cases tuberculosis is suspected as in this one, but a certain confirmation of diagnosis cannot be made from Roentgen films, tuberculin tests and sputum examinations.

Pneumonia is easily identified in the presence of cysts, but very frequently the cyst causes suspicion of cavity or abscess formation. Gibson,[6] by introducing lipiodol, was able in his case to demonstrate the cysts and a fluid level in them by changing the posture of the patient. In the usual Roentgen ray films the cysts appear in varying density as oval or circular areas of lessened density, often surrounded by a sharply defined margin, which may be interpreted as pneumothorax and be aspirated. Clairmont[7] calls attention to the fact that an interlobar line often may be seen crossing a cyst, but not a pneumothorax. Cysts, unless very large do not give any very definite physical signs, but the pneumonia which surrounds them indicates itself in the usual manner.

Treatment of the cysts is not very satisfactory. Inasmuch as 35 of Koontz's collected cases lived 30 years or more, and 1 to the age of 84, it may be accepted that the condition is not always fatal at an early age. Operation has been attempted in a number of instances. Clairmont operated upon a boy of 10, removing a cystic middle lobe, but the patient died of postoperative shock. Sauerbruch[8] resected cystic lobes in 4 adult cases diagnosed empyema, all of whom recovered. R. T. Miller[9] reports a patient of 5 weeks into whose cyst was inserted a one-way air valve; this patient lived comfortably for several months, but then suddenly died. From these observations it may be concluded that cystic disease is of graver import in early life and that operative procedures at this age are at the present time of considerable danger.

Comment. The English authors have attributed the cysts to bronchopneumonia and atelectasis occurring after birth. The progressive increase in the size of the cavities demonstrated roentgenographically in this case indicates that changes were continuing during the period during which it was under observation. In several of the cavities direct communication with a bronchus could be demon-

strated. In the cavities in the left upper lobe this communication was found at necropsy, but could not be found after hardening in formalin. In the large cyst between the left lower lobe and the anomalous left middle lobe formation no communication could be found at any time. In fact, this cyst was immersed beneath the surface of formalin for 1 year without the slightest deflation or loss of air content. It is to be presumed that its communication was by means of a very narrow channel, allowing the access but not the egress of air. deLange[10] has postulated three methods of origin of these cysts:

1. A fetal bronchial inflammation with valvelike stenosis of the bronchioles. This she believes to be almost invariably syphilitic.

2. A hyperplastic condition in which an excess of tissue occurs. In some of the cases in this category there is found bronchial overgrowth and cystadenomatous formation difficult to attribute to mere bronchial dilatation.

3. A hypoplastic condition in which the alveolar tissues have failed to develop and in which bronchial enlargement has taken place in compensation therefor.

We believe the cysts in our case are of congenital origin because of their smooth lining wall and because of the presence of a flattened atypical lining epithelium. The presence of an anomalous lobe lends support to this view. Furthermore, the presence of certain acinus-like formations seen in one of the sections indicates an element of hyperplasia of tissue, which we believe to be a defect in embryonal development. In addition to this factor, we believe that a mechanical factor, gradual inflation of the cyst has been operative since respiration began.

Summary. A case of congenital cystic disease of the lung in an infant of 4 months is presented, with roentenographic studies and necropsy findings. Progressive enlargement of the cysts is visualized in serial films. Microscopic findings suggestive of abnormal embryonic development are described.

REFERENCES.

1. Koontz, A. R.: Congenital Cyst of the Lung, Bull. Johns Hopkins Hosp., **37**, 340, 1925.

2. Stoerk, O.: Ueber angeborene blasige Missbildung der Lunge, Wien. klin. Wchnschr., **10**, 25, 1897.

3. Couvelaire, M. A.: Degenerescence kystique congenitale, Rev. mens. d. mal. de l'enf., **22**, 60, 1904.

4. Eloesser, L.: Congenital Cystic Disease of the Lung, Surg. Clin. North America, **8**, 1361, 1928.

5. Anspach, W. E., and Wolman, I. J.: Large Pulmonary Air Cysts of Infancy, Surg., Gynec. and Obst., **56**, 635, 1933.

6. Gibson, D. N.: Congenital Cystic Lung, Am. J. Roentgenol., **28**, 155, 1929.

7. Clairmont, P.: Die geschlossene intrapulmonale Bronchuszyste, Deutsch. Ztschr. f. Chir., **200**, 157, 1927.

8. Sauerbruch, F.: Zur Frage der Entstehung und chirurgischen Behandlung von Bronchiektasen, Arch. f. klin. Chir., **148**, 721, 1927.

9. Miller, R. T., Jr.: Congenital Cystic Lung, Arch. Surg., **12**, 392, 1926.

10. deLange, C.: Angeborene Zystenlunge and agenctische Bronchiectasie, Acta Pediat., **6**, 352, 1927.

FACTORS AFFECTING THE APPEARANCE AND DURATION OF GLYCOSURIA.*

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The present work is an attempt to correlate the blood sugar level with the appearance and disappearance of glycosuria and to study the factors which control the excretion of sugar in the urine. An intravenous tolerance test was used in which an amount of glucose just sufficient to produce glycosuria was injected. In order to correlate accurately the blood sugar level with the time of appearance and disappearance of glycosuria, capillary blood specimens were collected at frequent intervals and simultaneously urine specimens were obtained by catheter which was kept in the bladder throughout the experiment. Only women subjects have been studied because of the ease of catheterization.

Procedure. Our procedure was as follows: After an all-night fast a catheter was placed in the bladder with sterile technique. A preliminary blood specimen was collected and the bladder emptied. Glucose in 50% solution was injected rapidly into the arm vein, usually during 30 to 60 seconds. Urine samples were collected from the catheter at minute intervals for the first 15 minutes and later at somewhat longer intervals, while capillary blood samples were collected from the ear at 1- to 3-minute intervals for 6 minutes and then at 6-minute intervals until the end of the experiment. Qualitative tests for sugar in urine were run in every case to assure the continuance of the experiment until after the disappearance of glycosuria and in most cases the sugar excretion was determined quantitatively. Blood sugar analyses were done by the micromethod of Folin as modified by Folin and Malmros,[8] and the urine specimens were analyzed by Benedict's qualitative and quantitative methods.[7]

Ten grams of glucose were given in most of the tests as it was found that this amount could be relied upon to produce a glycosuria of moderate duration. The figure was arrived at from preliminary experiments, using doses varying between 3 and 8.8 gm., which frequently failed to produce glycosuria at all, and doses of 12 to 20 gm., which produced greater hyperglycemia and prolonged glycosuria.

The results of the analysis of blood and urine were plotted and the blood sugar values at which glycosuria appeared and disappeared were determined

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by interpolation. For instance, in Patient "ST" the urine collected in the fourth minute after injection was positive for sugar. The corresponding point on the blood sugar curve was 148 mg. per 100 cc. The urine specimens continued to be positive for sugar for 25 minutes, while the specimens collected at 29 minutes and thereafter were negative. The blood sugar concentration at 29 minutes by interpolation from the curve was 101 mg. per 100 cc.

Thirty series of observations were carried out on patients in the Vanderbilt University Hospital who had no known abnormality in carbohydrate metabolism or renal function. In each case a similar type of curve of blood sugar concentration was obtained. The first specimen, taken from 1 to 3 minutes after injection was completed, showed a maximum value from which the concentration rapidly fell. The blood sugar values found before injection were all in the normal range. Such variations as occurred within this range showed no relation to subsequent values and hence are omitted from the table. While it is true that urine is formed from plasma and our results were obtained with whole blood, the equilibrium between cells and plasma is established with such rapidity that only in the first sample of blood taken after injection could this element of uncertainty be noticeable. To have carried out the analyses on plasma would have necessitated sacrifices in other more important factors in the experiments.

Appearance Time of Glycosuria. When glucose is administered by mouth there appears to be a definite delay in its appearance in the urine which may amount to over one-half hour. This phenomenon after orally administered glucose has been called, perhaps inaccurately, the renal lag, and while noted by earlier observers was first emphasized by Faber and Hansen.[1] During this interval preceding glycosuria the peak of the blood sugar values is usually passed and the hyperglycemia begins to wane. The reason for this is not known, but in the words of Faber and Hansen, "It seems to be an expression of the effort of the kidneys to avoid the excretion of sugar as far as possible."

When an adequate dose of glucose is administered intravenously it appears in the urine very quickly, partly perhaps because some of it is carried directly to the kidney without first going to the liver as does ingested glucose. In our series of 30 cases, glycosuria set in in 5 minutes or less in 14 cases. The renal lag was consequently very small and was partly accounted for by the time required to fill the ureters, bladder and catheter. Nevertheless, it seems that even with intravenously administered sugar a definite interval of time over and above that necessary for simple excretion as determined with non-threshold substances elapses between the presentation of a quantity of sugar to the kidney and its appearance in the urine. Furthermore, frequently this excretion does not start until the blood sugar values are decreasing.

TABLE 1.—THRESHOLD VALUES AND RENAL LAG.

Patient.	Fluid, cc.	Glucose given, gm.	Glucose excreted in urine, gm.	Injection time, sec.	Glycosuria.			Urine.		Blood sugar level (per 100 cc. capillary blood)			
					Appearance, min.	Disappearance, min.	Duration, min.	Vol., cc.	Rate.*	Peak, mg.	Accuracy.	Appearance, mg.	Disappearance, mg.
St.	..	10.0	0.31	28	4	29	25	56	1.3	150	−	148	101
Car.	..	10.0	0.12	22	11	25	14	183	5.2	162	+	123	102
Wi.	..	10.0	0.09	50	5	25	20	108	2.7	179	−	159	110
Pr.I	..	10.0	0.12	54	7	>48	>41	25	0.5	169	+	168	100†
Pr.II	1000	10.0	0.15	37	4	9	5	310	10.3	173	−	168	152
Du.‡	..	10.0	0.09	50	5	33	28	311	5.1	131	−	121	82
Ha.I	..	5.0	0.00	20	..	..	..	64	1.7	152	−		
Ha.II	..	7.5	0.01	30	8	15	7	138	2.8	160	+	138	109
Ha.III	..	10.0	0.06	45	5	32	27	75	1.6	198	−	193	139
Jo.	..	10.0	0.10	77	4	16	12	109	2.6	246	+	204	168
Ba.	..	20.0	1.36	240	< 4	25	>25	226	2.7	494	−	494	324
Ham.I	..	3.0	0.00	30	..	..	..	27	0.7	134	−		
Ham.II	..	12.0	0.13	60	5	26	21	108	1.4	398	+	330	162
Gr.	..	10.0	0.20	60	6	21	15	152	1.1	304	+	230	182
Br.	..	12.0	0.20	60	< 8	25	>15	42	0.8	220	+	204	139
Ral.	..	10.0	0.13	42	15	51	36	103	1.7	196	+	154	125
La.I	..	10.0	0.13	35	4	29	25	57	1.3	177	+	155	120
La.II	1000	10.0	0.15	30	4	9	5	111	4.6	219	+	170	150
La.III	1000	10.0	0.16	34	3	12	9	74	2.9	194	−	181	150
Hi.I	..	7.5	0.00	22	..	..	..	71	2.4	147	−		
Hi.II	*ad lib.*	10.0	0.10	45	4	13	9	102	2.8	176	−	172	154
Hi.III	*ad lib.*	8.8	0.07	40	13	17	4	15	0.5	200	+	172	158
Hi.IV	*ad lib.*	10.0	0.15	34	6	17	11	78	2.4	209	+	188	170
Be.	..	6.0	0.00	25	..	..	..	21	0.8	138	−		
Se.	..	10.0	0.00	31	..	..	..	89	3.7	172	−		
Cu.	..	10.0	..	60	4	>48	>44	40	0.8	304	−	294	
Can.I	..	8.0	..	90	32	>44	>12	24	0.5	210	+	139	
Can.II	..	12.0	..	120	<14	>38	>24	32	1.3	290	+	189	
Bo.I	1000	10.0	0.00	60	..	..	..	402	21.2	252	−		
Bo.II	..	10.0	0.21	40	4	29	25	75	2.2	252	+	226	159

* Cc. per minute.

† Blood sugar concentration at 48 minutes.

‡ This patient was suffering from general paresis and a variety of other things so that any anomalies in the results must be discounted because of her extremely poor state of health.

With our standard dose of 10 gm. of glucose the renal lag equalled or exceeded 7 minutes in 3 experiments. The phenomenon is, however, influenced by constitutional and other factors. Thus occasional values much in excess of this are found even when smaller doses of glucose are used. As may be seen from Table 1, a lag of 32 minutes occurred in Patient "Can." after a dose of only 8 gm. This patient was interesting because when the dose was increased to 12 gm. the beginning of excretion was still delayed for

almost 14 minutes. Apparently this was a personal trait. In the case of another patient (Hi.III), a delay of 13 minutes may have been due to an almost complete anuria.

Previous investigators have called attention to the fact that glycosuria frequently does not set in until after the maximum blood sugar level has been passed.[1,9] Our experience agrees with this finding. While the peak was always passed in our experiments using the intravenous method, sugar did appear in the urine while the blood sugar values were rising in some (unreported) experiments in which sugar was given diabetics by mouth. An examination of the results of other observers as presented in the literature reveals a similar lack of uniformity. There appears to be no relationship between the attainment of the maximum hyperglycemic level and the appearance of glycosuria. That glycosuria can play but little part in the reduction of the hyperglycemia is evident from the figures in Table 1, showing the actual amount of sugar that escaped in the urine in several of our cases. The maximum amount recovered was 7%.

The Appearance Level of Glycosuria. The term threshold is usually defined as the concentration of sugar in the blood at which glucose appears in the urine in quantities sufficient to respond to the usual tests. It should be clearly understood, however, that this definition refers to the *minimum* concentration at which sugar *can be made* to appear by the administration of carbohydrate. In experiments of our own and of others[9] glycosuria was made to appear in normal people at much higher levels. In fact, it seems to be possible to produce it at almost any level above the true threshold, by the injection into normal people of large enough doses of glucose and in diabetics by its oral administration. Thus in 1 of our patients 20 gm. of glucose gave an appearance level of 494 mg.% and this was probably submaximal. It is obviously not the true threshold. In another case a 12-gm. dose gave an appearance level of 189 mg.%, but 8 gm. of glucose resulted in glycosuria only at 139 mg.%.

For determining the true threshold, Faber's scheme[1] of using two doses of glucose, one of which just fails to produce glycosuria and another slightly larger dose which results in a brief excretion of sugar appears to be the more accurate one. Our values cannot be considered as thresholds in the true meaning of the term. We were interested not in determining the true threshold, but in studying the factors which alter the blood sugar concentration at which glycosuria appears.

Nevertheless, because of the size of the dose selected, the values with our standard dose fall in the range of threshold values found by previous observers, Peters and Van Slyke,[6] giving an approximate range of 140 to 200 mg.%.

Judging from the slopes of the curves the actual maximum values

attained by the blood sugar were probably momentary, occurring during or immediately after injection, and only by chance could they have coincided with the taking of the samples of blood. There was some slight variation in the injection rate, and from 1 to 5 minutes were required for obtaining the first blood specimen. The blood sugar maxima observed with 10 gm. of injected glucose varied considerably, ranging from 131 to 304 mg.%, and for the above reasons give no idea of the true maxima. Since the first blood sugar values were submaximal, it was not possible to calculate a value for the beginning of glycosuria if sugar was already present in the urine when the first blood sample was collected. Only when sugar appeared in the urine between two blood sugar values on the descending branch of the curve could its appearance in the urine be accurately correlated with the blood sugar level. Nine of our cases to which a dose of 10 gm. was given and 6 to which larger or smaller doses were administered showed this picture. Such samples are marked "+" in the column headed "Accuracy" in Table 1.

The blood sugar concentration at the appearance of glycosuria in those patients receiving 10 gm. of glucose varied from 123 to 230 mg.%, but in 6 of the 9 cases was between 154 and 204.

The question of the constancy of the threshold in individuals has been thoroughly discussed in the papers of Faber and Hansen,[1] Sakaguchi[9] and others. As the above authors have pointed out, much confusion has arisen from the crudeness of the methods used. Table 2 shows the results of duplicate determinations on each of

TABLE 2.—RANGE OF VARIATIONS OF DUPLICATE DETERMINATIONS ON THE SAME SUBJECT.

	I (La.II and III).		II (Hi.II and IV).	
	(1)	(2)	(1)	(2)
Appearance time of glycosuria, min.	4	3	4	6
Blood sugar at appearance of glycosuria, %	170	181	172	188
Blood sugar at disappearance of glycosuria, %	150	150	154	170
Volume of urine, cc.	111	74	102	78
Duration of glycosuria, min.	5	9	9	11

2 patients. With our technique it is apparently possible to reproduce the appearance of glycosuria within 10 to 15 mg.%. This appears to represent the experimental error of the method. Hence, threshold values agreeing within this range can be considered constant and they indicate that our method of procedure does give results reproducible within this range.

In the cases where doses larger or smaller than 10 gm. were injected the appearance levels tended to become respectively higher or lower so that the higher the concentration of the sugar is raised in the blood the higher the value at which glycosuria will appear.

The Disappearance Level of Glycosuria. Our disappearance levels were always lower than the appearance levels and covered a wider range. In 7 of 21 cases they were at or below 120 mg.%, *i. e.*,

in the normal aglycosuric range. As others have pointed out,[1,9] the disappearance level of glycosuria does not appear to be an accurate criterion of the ability of the kidney to hold sugar, although there seems to be a certain correlation between the heights of the appearance and the disappearance levels. The correlation index is 0.85 but, because of the small number of samples available, is of doubtful significance. Our impression is that with increased doses of glucose the whole glycosuric range is pushed up on the blood sugar scale. This means that the greater the hyperglycemia produced in a tolerance test, the higher the level at which glycosuria will begin and end.

The Duration of Glycosuria. In 2 of our 19 experiments using 10 gm. of glucose there was no glycosuria; in 8 the duration was 15 minutes or less; in 4 it was between 15 and 26 minutes; in 3, between 26 and 37 minutes; and in 2 others the glycosuria had not ceased at the end of over 40 minutes when the experiments terminated. The fact that in these last experiments very small amounts of urine were voided indicated that the duration of glycosuria might depend in part upon the volume of urine produced or the speed with which it was put out.

As a result of this observation, 1000 cc. of fluid were given by mouth to 1 patient during the 2 hours preceding the test. Her urinary output upon the first occasion was 23 cc., but with the fluids it was raised to 310 cc. and the disappearance of glycosuria was reduced from more than 40 to 5 minutes. Another patient who received no fluids showed glycosuria for 25 minutes and a urine volume of 57 cc. In 2 subsequent experiments this period was reduced to 9 and 5 minutes with urine volumes of 74 and 111 cc. respectively by the administration of 1000 cc. of fluid. One patient who seemed to fall entirely out of line voided only 15 cc. of urine, the smallest amount in the series, and showed glycosuria for only 4 minutes. She had received only 8.8 gm. of glucose. She had been allowed fluids *ad lib.*, but as the actual amount taken was not measured, no point can be made of the result. A statistical analysis of our cases showed an index of correlation between the volume of urine and the duration of glycosuria of 0.6542 ± 0.0863, a figure of uncertain significance with such a small number of cases. There was no demonstrable relationship between the duration of glycosuria and the appearance time, perhaps because the latter was usually so short that the error in determining it obscured any variation that might have occurred.

One factor, not capable of perfect control, was the completeness with which the bladder, kidney, pelvis, etc., was emptied at each sample. This, if not done, could extend the disappearance time and hence the duration. Some of the irregularities may be explained on this basis, although the greatest care possible was used in attempting to clear the bladder of urine at each collection.

Discussion. Our results from the intravenous injection of doses of glucose varying from 7.5 to 20 gm. may be summarized as follows: Usually 3 to 8 minutes were required for the appearance of glycosuria but not infrequently this period was lengthened, and in 1 case no sugar appeared in the urine until 32 minutes after injection. During this time the blood sugar values had passed the maximum and were diminishing. With the same dose, the appearance level was constant for an individual but varied with different people. With the same person it varied with the dose. The disappearance level was lower than the appearance level and while less constant, it did depend to some extent upon the latter value. The smaller the volume of urine voided, or the slower the rate, the longer did glycosuria persist.

In the absence of definite knowledge of the mechanism involved, speculation is more or less futile, but it may be presumed that the tubular absorption of glucose may for a while be able to remove the increased quantity in the glomerular filtrate. After a period of variable duration the absorptive power weakens and glycosuria ensues.

Höber has recently[2] recalled a suggestion originally made in 1899,[3] that glucose is absorbed by the formation of some intermediary compound in the tissues. Experimental evidence has recently been advanced,[4,5,12] indicating that this is one of the hexosephosphates and that absorption both from the alimentary tract and through the kidney tubules is dependent on this process. It has been shown that phlorizin acts by interfering with the formation or decomposition of this compound with a resultant excretion of sugar.[2,10] It would seem that the glycosuria produced in our experiments may have been due to a failure in the same process though a failure of a different nature.

In the glycosuria of phlorizin poisoning the tubular resorptive mechanism is so severely damaged that it either fails completely or if it functions at all it does so only at a greatly reduced efficiency. With hyperglycemic glycosuria there are two possibilities: (1) The mechanism may be as active as usual but simply unable to transport more than a fraction of the increased burden of glucose presented to it, leaving an excess to escape through the ureter, or (2) the capacity of the machine may be reduced by the exhaustion of one of its elements, *e. g.*, the phosphate or one of the enzymes involved. The second case resembles that of phlorizin poisoning, though in the latter an enzyme is apparently inactivated and not merely depleted.

If one makes the simplifying assumption that sugar passes through the glomerulus so rapidly that this process does not become a limiting factor in the subsequent events, the appearance of sugar in the urine, if the first condition holds, should take place as soon as the blood sugar has reached a point where the sugar in the urine

exceeds the capacity of the tubular absorptive mechanism to remove it completely. Since the urine is promptly carried beyond the tubules, glycosuria should cease as soon as the blood sugar level has fallen to the point where all of the sugar can be removed. In other words, since intravenous injection of glucose causes an almost instantaneous rise in blood sugar, the appearance of glycosuria should be very prompt in all cases where the proper height of blood sugar is reached. The delays of 3 to 8 minutes which were commonly found seem to be too long. There should be no noticeable difference in appearance time since the time required to reach the blood sugar peaks were identical within our ability to measure them.

The disappearance levels should coincide with the appearance levels. And since the blood sugar was changing much more slowly when glycosuria disappeared, and hence these figures could be caught more accurately, they should be more constant than the appearance values. The opposite was found.

On the other hand, if some element in the system had to be used up this might require not only a measurably long period but also one which would vary with the supply of the material present, the rapidity with which it could be restored and the rapidity with which it was being exhausted, *e. g.*, from a continued high blood sugar. Also since in any case time would be required for its replacement, a lag in the disappearance level of blood sugar would result. In other words the appearance of glycosuria should lag behind the injection and the disappearance level should be lower than the appearance level. It should be more variable but with some degree of dependence upon it.

Finally, under the first condition the slower the flow of urine, the more completely could the sugar be removed and the more rapidly would glycosuria disappear. A slow secretion could compensate for a high sugar concentration. On the other hand, if the renewal of the sugar-absorbing mechanism depended on the replacement of some constituent supplied by the urine, *e. g.*, inorganic phosphate, the longer would glycosuria continue if the supply of urine were reduced. This is what does happen.

If one accepts the suggested part of phosphorylation in glucose absorption, a new significance is given to the results of Wilder and Sansum,[11] who found that glucose could be injected at the rate of 0.85 gm. per kilo per hour without glycosuria. This may represent a maximum rate at which the phosphorylation mechanism can operate. In our cases of hyperglycemic glycosuria this maximum rate was exceeded, some element in the phosphorylation mechanism, such as the store of phosphate or of enzyme in the tubular membranes, became exhausted, adequate resorption of glucose was prevented, and sugar appeared in the bladder urine.

Conclusion. A study of the relationships between hyperglycemia and glycosuria after the intravenous injection of glucose indicates

that the excretion of sugar may be explained on the basis of the suggested participation of phosphorylation in the resorption of glucose from the glomerular filtrate.

REFERENCES.

1. Faber, K., and Hansen, K. M.: Threshold of Glycosuria and Errors Involved, Acta med. Scand., **58**, 372, 1923.
2. Höber, R.: The Excretion of Sugar by the Isolated Frog Kidney, Pflüger's Arch., **233**, 181, 1933.
3. Höber, R.: Resorption in the Small Intestine, Ibid., **74**, 246, 1899.
4. Lundsgaard, E.: Inhibition of Esterification Processes as the Cause of Phlorizin Activity, Biochem. Ztschr., **264**, 209, 1933; The Effect of Phlorizin on Glucose Resorption, Ibid., p. 221.
5. Nilsson, R.: The Glycolytic Degradation of Carbohydrates, Ibid., **258**, 198, 1933.
6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Interpretations, Baltimore, The Williams & Wilkins Company, **1**, 134, 1932.
7. Peters, J. P., and Van Slyke, D. D.: Ibid., Methods, **2**, 446, 1932.
8. Peters, J. P., and Van Slyke, D. D.: Ibid., p. 464, 1932.
9. Sakaguchi, K., *et al.*: Threshold of Sugar Output in Diabetics, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, **32**, 61, 1924.
10. Wertheimer, E.: The Effect of Phlorizin on Sugar Resorption, Pflüger's Arch., **233**, 514, 1933.
11. Wilder, R. M., and Sansum, W. D.: d-Glucose Tolerance in Health and Disease, Arch. Int. Med., **19**, 311, 1917.
12. Wilbrandt, W., and Laszt, L.: Investigation of the Cause of Selective Resorption of Sugar From the Intestines, Biochem. Ztschr., **259**, 398, 1933.

VARIATIONS IN BLOOD PRESSURE IN RENAL TUBERCULOSIS.

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The opinion is generally expressed[6,7] that patients who have an active tuberculous lesion usually exhibit an arterial tension lower than normal regardless of the situation of that lesion. For that reason we were interested to determine what the ranges of blood pressure would be among subjects who had renal tuberculosis, inasmuch as a study of an adequate series from this standpoint had not been reported in the literature. Ayman stated that arteriolar essential hypertension and active tuberculosis do not commonly occur together, but he offered no explanation for this. A recent analysis of the blood pressures of tuberculous patients encountered in dispensary practice was made by Bunta, who commented on his findings by saying that progressive lowering of the blood pressure paralleled tuberculous activity. He felt that hypotension was not an absolute rule in tuberculosis, but that the trend of individual measurements of blood pressure toward normal spoke

well for the ultimate arrest of the disease, and that a progressive lowering of the blood pressure called for a guarded prognosis.

It has been postulated[3] that action of the tuberculous toxin on the vasodilator center is the factor which results in an arterial tension lower than normal in tuberculous patients. Fishberg[5] stated that "blood pressure is lower than normal in the vast majority of phthisical patients, evidently due to the toxic effects of the metabolic processes of the tubercle bacillus, because an injection of tuberculin is usually followed by a fall in blood pressure."

TABLE 1.—SYSTOLIC BLOOD PRESSURES OF 229 MALES WITH RENAL TUBERCULOSIS.

Systolic blood pressure, mm. mercury.	Age, yrs.													
	10 to 14.	15 to 19.	20 to 24.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	Total.	Per cent.
90 to 99	..	..	..	..	..	1	..	..	..	..	..	..	1	0.4
100 to 109	..	..	..	3	6	2	4	6	4	..	..	1	26	11.4
110 to 119	..	3	4	11	13	8	5	5	2	3	1	..	55	24.0
120 to 129	3	5	7	6	9	11	8	4	5	1	..	..	59	25.7
130 to 139	..	2	1	4	8	7	6	7	1	2	..	..	38	16.6
140 to 149	..	..	3	..	5	7	3	1	5	3	..	..	27	11.8
150 to 159	..	..	2	..	1	..	..	1	2	..	2	..	8	3.5
160 to 169	..	..	1	..	..	1	1	1	2	1	..	..	7	3.0
170 to 179	..	..	..	1	..	1	..	1	..	..	1	..	4	1.7
180 to 189	..	..	..	..	..	1	..	1	..	1	..	..	3	1.3
190 to 199														
200 to 209														
210 to 219	..	..	..	..	..	..	..	1	..	..	..	..	1	0.4
Average . .	124	123	130	120	121	128	124	130	129	136	147	102	126.9	
Total patients .	3	10	18	25	42	39	27	28	21	11	4	1	229	

We analyzed the systolic blood pressures in 346 unselected cases of renal tuberculosis in which patients were admitted to The Mayo Clinic between 1925 and 1934, inclusive (Tables 1 and 2). Nephrectomy was carried out in each case and in each case the clinical diagnosis of renal tuberculosis was substantiated. Of the 346 patients, 117 were females and 229 were males, their ages ranging from 11 to 68 years. The left kidney was involved in 167 cases, the right in 169 cases and in 10 cases both kidneys were involved. Acid-fast bacilli were isolated from the urine in 258 cases (74.5%). The renal lesion was active in every case, which was demonstrated at the time of nephrectomy, and there was almost complete destruction of the involved kidney in most cases. Adequate renal function was the rule, as was evidenced by the fact that of 245 cases in

which the blood urea was estimated, in only 27 was the value more than 40 mg. per 100 cc.

TABLE 2.—SYSTOLIC BLOOD PRESSURES OF 117 FEMALES WITH RENAL TUBERCULOSIS.

Systolic blood pressure, mm. mercury.	Age, yrs.													
	10 to 14.	15 to 19.	20 to 24.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	Total.	Per cent.
80 to 89	..	1	..	..	..	..	..	..	..	..	..	..	1	0.9
90 to 99	..	..	..	1	1	1	1	..	..	..	..	..	4	3.4
100 to 109	..	2	1	2	5	1	4	..	..	..	..	..	15	12.8
110 to 119	..	..	6	1	9	5	2	2	2	..	..	1	28	23.9
120 to 129	..	..	1	5	7	9	1	4	2	1	1	..	31	26.5
130 to 139	..	..	1	1	2	1	3	1	2	2	..	..	13	11.1
140 to 149	..	..	..	1	3	1	2	1	2	..	..	1	11	9.4
150 to 159	..	..	..	1	1	..	..	1	1	..	..	..	4	3.4
160 to 169	..	..	..	..	..	..	1	2	2	1	..	1	7	6.0
170 to 179	..	..	..	..	..	..	1	..	..	..	..	..	1	0.9
180 to 189	..	..	..	..	..	..	..	2	..	..	..	..	2	1.7
190 to 199														
200 to 209														
210 to 219														
Average . .	..	99	115	121	119	120	125	141	138	139	120	137	124.5	
Total patients .	..	3	9	12	28	18	15	13	11	4	1	3	117	

A systolic blood pressure of between 100 and 140 mm. of mercury was regarded as normal. Of the males, 77.7% and of the females, 74.4% had systolic blood pressures in this normal range. The systolic blood pressures of 21.8% of the males and of 21.4% of the female was 140 mm. of mercury or more; 0.4% of the males and 4.3% of the females had a systolic pressure less than 100. In Figs. 1 and 2 the actual readings of systolic blood pressure for each of the 229 males and 117 females, respectively, are recorded. The mean value for each age group was superimposed in the form of a curve, and for purposes of ready comparison we have added a control curve, obtained by an analysis of the systolic blood pressures of 1668 normal males and 1202 normal females.* It is obvious that the average systolic blood pressures of males and females who have renal tuberculosis closely parallels the average readings for normal individuals, and when plotted as a graph form a gently upswinging curve, for the most part lying between the limits of 120 and 130 mm. of mercury and reaching its peak in the upper age groups.

In a consideration of the whole group, 265 patients (76.58%) had a systolic blood pressure reading between 100 and 139 mm. of

* Unpublished work by Alvarez and Berkson of The Mayo Clinic.

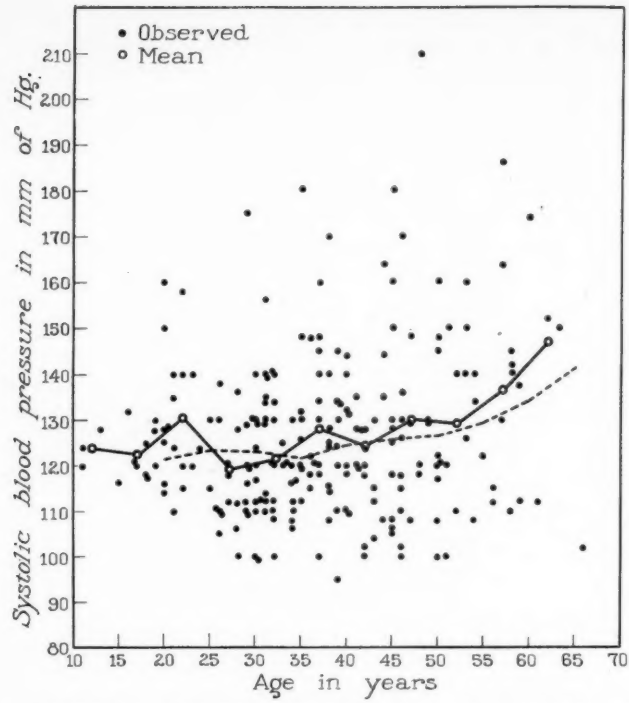

FIG. 1.—Systolic blood pressures of 229 males with renal tuberculosis. The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of 1668 normal males.

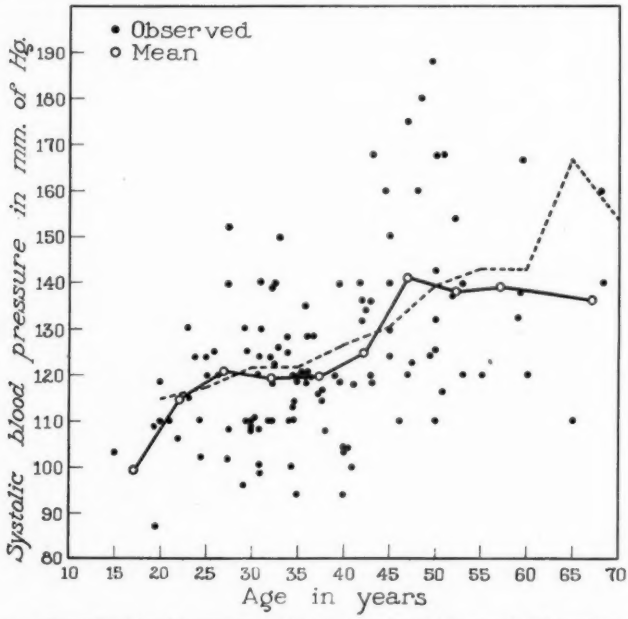

FIG. 2.—Systolic blood pressures of 117 females with renal tuberculosis. The continuous line is the curve of the mean systolic blood pressures. The broken line is a curve representing the mean systolic blood pressures of 1202 normal females.

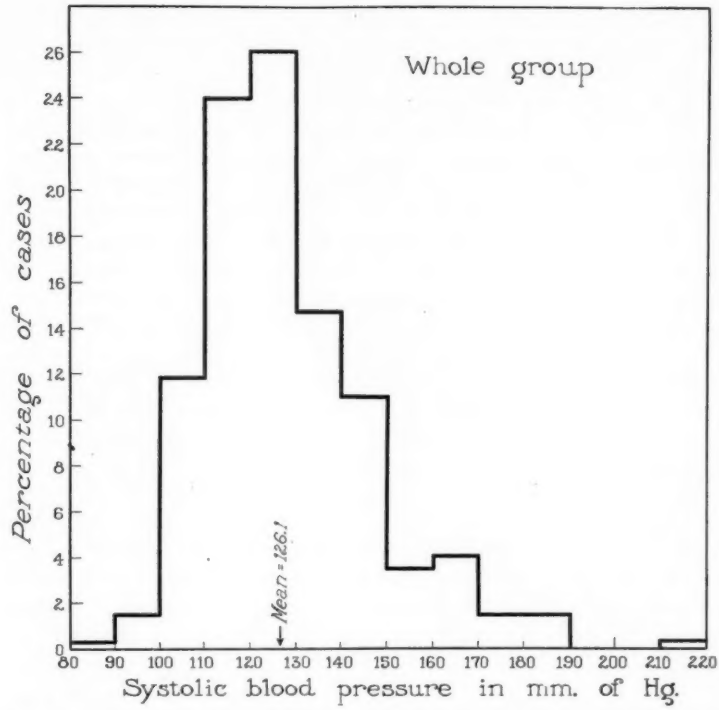

FIG. 3.—Percentage incidence of various levels of systolic blood pressure (in units of 10 mm. of mercury) in the whole group of 346 patients who had renal tuberculosis.

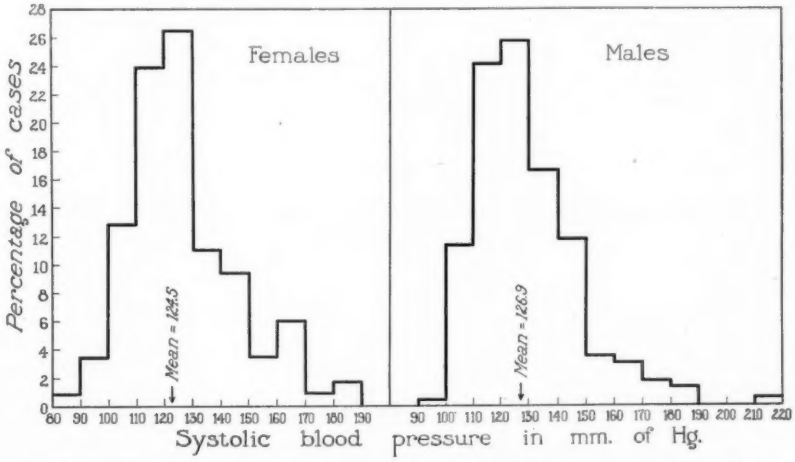

FIG. 4.—Percentage incidence of various levels of systolic blood pressure (in units of 10 mm. of mercury) in 229 males and 117 females who had renal tuberculosis.

mercury, inclusive; 6 (1.72%) had a reading less than 100; and 75 (21.64%) had a reading of 140 or higher. The lowest reading recorded was 86, the highest 210. The mean value for the whole group, obtained by averaging the recorded values, was 126.1 (Fig. 3). When a further consideration was made of males and females separately, there was found to be no essential sex variation (Fig. 4); 77.7% of the males and 74.4% of the females had a systolic blood pressure ranging between 100 and 139 mm. of mercury. The mean systolic value for the males was 126.9 and for the females 124.5.

Summary. As a result of the analysis of the systolic blood pressures of 346 patients who had proved renal tuberculosis, we cannot concur in the opinion generally expressed, that an active tuberculous lesion, regardless of its situation, has an accompanying arterial tension lower than normal. In the series of cases analyzed it was found that the vast majority of patients (approximately 76%) had normal blood pressures, 22% had hypertension, that is, a systolic pressure of 140 mm. of mercury or more, and approximately 2% had hypotension, that is, a systolic blood pressure less than 100 mm. of mercury. The number of patients in this series with hypertension or hypotension was not any greater than was found in a larger control series of normal individuals in the same age groups.

BIBLIOGRAPHY.

1. Alvarez, W. C., and Berkson, J.: Personal Communication.
2. Ayman, D.: Arteriolar Essential Hypertension and Active Tuberculosis: Their Rare Association, Am. J. Med. Sci., **188**, 712, 1934.
3. Brelet, M., and Perrin, P.: Hypertension artérielle et tuberculose, Gaz. d. hôp., **101**, 469, 1928.
4. Bunta, E.: Blood Pressure Variations in Tuberculosis: A Statistical Study of the Range of Arterial Tension, Am. Rev. Tuberc., **29**, 335, 1934.
5. Fishberg, M.: Pulmonary Tuberculosis, 3d ed., Philadelphia, Lea & Febiger, p. 228, 1922.
6. Marfan, A. B.: La tension artérielle dans la tuberculose pulmonaire chronique et son importance pour le pronostic, Rev. de méd., **27**, 1005, 1907.
7. Stivelman, B. P.: Observations on the Blood Pressure in Pulmonary Tuberculosis, Am. J. Med. Sci., **173**, 46, 1927.

FACTORS CONDITIONING THE TRANSMISSION OF SYPHILIS BY BLOOD TRANSFUSION.*

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It is a well established fact that the virus of syphilis may be transmitted by blood transfusion. A recent incident in my own

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experience has emphasized the necessity of clarifying our knowledge concerning this therapeutic accident. A colleague is involved in litigation as the result of having given a transfusion with blood from a donor who later was found to have syphilis. The recipient subsequently was also found to have syphilis and a malpractice suit was instituted on the grounds that the disease had been acquired through the medium of the blood transfusion. In this instance the importance of being able to say what is and what is not "transfusion syphilis" is obvious. While a good deal has been written on the subject, most of the papers in the literature consist of case reports. In the present study an effort was made to analyze the data and to relate the information thus obtained to our knowledge of the human and experimental disease. It was done with the hope that the knowledge thus acquired would make it possible to define clearly the clinical features of "transfusion syphilis" and to state the circumstances under which it may develop.

Material. In 1915 Fordyce first recorded the transmission of syphilis by blood transfusion. Bernheim in 1917 gave an undetailed account of its occurrence once in his experience.[1] In recent years cases have been reported with increasing frequency. These have been reviewed and tabulated and an additional case from the Vanderbilt University Hospital added (Table 1.) Several reports in the literature were not considered to have been founded on conclusive evidence, or were too incomplete to allow for analysis, and were therefore not included.

In all there were found to be 16 indubitable cases of syphilis acquired through blood transfusion. In every instance the disease made itself apparent by the development in the transfusion recipient of generalized lesions (skin, mucous membranes). In all instances in which the incubation period could be determined, it was found to be between 4 and 14 weeks. Every case of "transfusion syphilis" apparently developed the picture of the generalized, secondary stage of the disease and this within from 1 to $3\frac{1}{2}$ months after the transfusion. The literature contains no instance of latent or active chronic syphilis which was acquired through blood transfusion without having passed through a readily recognizable acute stage. It would seem that the introduction of the virus directly into the blood stream invariably results in acute manifestations of the generalized infection.

An analysis of the table as regards the donors is enlightening. The status of syphilitic infection in the donors could be determined in 11 of the 16 reports analyzed. Of these 11 donors 9 had either primary or secondary syphilis at the time of the transfusion. Another donor gave blood 4 days before the appearance of the chancre. Thus 10 of the 11 donors had acute syphilis. In 1 instance (Spillman and Morell) the blood donor was presumably infected by the recipient's blood through an interchange of cannulæ. The

recipient, a woman, subsequently died of postpartum hemorrhage. She had had 3 miscarriages and her husband was known to have syphilis. With the single exception, then, of syphilis related to pregnancy all of the donors whose syphilitic status could be determined had early, acute syphilis. Not a single instance of indubitable "transfusion syphilis" has been reported in which the disease was induced by blood from a donor with well established latent or chronic syphilis uninfluenced by pregnancy.

TABLE 1.—DATA IN 16 CASES OF TRANSFUSION SYPHILIS.

Author.	Type of syphilis present in donor ("acute" indicates primary or secondary stage).	Incubation period in recipient.	Clinical manifestations of syphilis in recipient.	Reference.
1. Fordyce, J. A.	Acute syphilis	Not stated	Generalized eruption	AM. J. MED. SCI., **149,** 781,1915
2. Brem, W. V.	Acute syphilis	Not given	Generalized eruption, presumably. Described as "virulent" syphilis	J. Am. Med. Assn. (Discussion) **81,** 535, 1923
3. Spillman, J., and Morell,	Generalized eruption developed 1 month after transfusion	One month	Chronic syphilis;* pregnancy	Bull. Soc. franç. de dermat. et de syph., **33,** 453, 1926
4. Levy, I. I., and Ginsberg, L.	Acute syphilis	2 to 3 months	Generalized eruption	Am. J. Syph., **11,** 447, 1927
5. Feldman, V.	Acute syphilis (recurrent secondary)	Within 3 mos.	Generalized eruption	Arch. Dermat. and Syph., **18,** 380, 1928
6. Constantinescou, E., and Vatamanu, N.	Acute syphilis	2½ months	Generalized eruption	Ann. d. mal. ven., **24,** 161, 1929
7. Aubertin, C., and Fleury, J.	Undetermined	9 weeks	Generalized eruption	Bull. et. mem. Soc. méd. d. hôp. de Paris, **54,** 69, 1930
8. Gougerot, Fiessinger, Bruno and Dally	Acute syphilis	3 months	Generalized eruption	Ann. d. mal. ven., **26,** 174, 1931
9. Polayes, S. H., and Lederer, M.	Undetermined	3½ mos. (approximate)	Generalized eruption	Am. J. Syph., **15,** 72, 1931
10. Pinard, M., and Robert, P.	Not determined; probably acute (laryngitis)	10 weeks	Generalized eruption	Bull. et. mem. Soc. méd. d. hôp. de Paris, **48,** 214, 1932
11. Post, C. D., and Cooney, G. C.	Acute syphilis, incubation stage; developed chancre 4 days after giving transfusion	3 months	Generalized eruption with meningeal signs	J. Am. Med. Assn., **100,** 258, 1933
12. Williamson, G. R. and Strong, R. A.	Not determined	6 weeks	Generalized eruption	Am. J. Syph., **17,** 484, 1933
13. Moore, J. E.	Acute syphilis (chancre)	4 to 6 weeks	Secondary syphilis	The Modern Treatment of Syphilis, Chas. C Thomas Baltimore, p. 456, 1933
14. Moore, J. E.	Acute syphilis (chancre)	4 to 6 weeks	Secondary syphilis	
15. Moore, J. E.	Not stated	5 weeks	Secondary syphilis	Cited by Moore, J. E.
16. Author's case	Acute syphilis	5 to 8 weeks	Secondary syphilis	

* In this case the transfusion donor received some of the recipient's blood, presumably through an exchange of cannulæ, and developed acute syphilis 1 month later.

Discussion. The relation of these clinical observations to other facts pertaining to both the experimental and human disease is enlightening. Since the virus of syphilis must be present in the blood of the donor if transfusion is to result in the establishment

of syphilitic infection in the recipient it would seem fitting to review first what is known concerning this point.

In the experimental disease in rabbits it has been shown that the virus of syphilis is present in the blood during the acute or active phase of the infection. With the disappearance of active lesions the blood loses its capacity to infect.[2] During latency, or inactive infection, the reservoir for Treponema pallidum is chiefly lymphoid tissue and not blood. This has been repeatedly demonstrated. That this is also true in the human disease was shown by Eberson and Engman[3] in 1921. Blood from 73 individuals with latent or chronic visceral syphilis was shown to be non-infectious when injected into rabbits' testicles. In a review of the literature these authors stated that the blood in chronic human syphilis had never been shown to be infectious for rabbits save in 1 case reported by Uhlenhuth and Mulzer.[4] This patient was a woman who had been delivered of a syphilitic fetus 18 days before the specimen of blood was obtained for examination. Moore[5] summarizes the matter as follows: "With the spontaneous healing of lesions it is probable that treponemes disappear from the blood to gain entry again, if at all, only in small and irregular showers during the period in which relapsing infectious lesions are prone to occur. After latency is firmly established the virus cannot be demonstrated by animal inoculation and it is probable that except in one special circumstance organisms are actually absent. The special circumstance is pregnancy. . . . . their presence in the mother's blood at some stage of pregnancy must be assumed."*

There is considerable evidence that not only will blood from individuals with chronic syphilis fail to induce the disease in rabbits but that it will also fail to transmit the disease to humans. Tzanck and Werth[6] record the case of a donor with seronegative latent syphilis who gave 18 transfusions without having once transmitted the disease to the recipients. This donor subsequently developed active neurosyphilis. It has been said that in Germany blood from cases of general paresis with *malaria inoculate* is frequently used in order to induce malaria in non-syphilitic patients.[7] There are no recorded instances of syphilis thus induced. McNamara[8] deliberately transfused 10 non-syphilitic patients with blood from 6 cases of chronic syphilis. In not a single instance was syphilis induced in the recipients, although 4 of the 10 received transfusions from 2 syphilitic donors and 1 recipient was transfused from 3 syphilitic donors.

While it is admittedly possible that syphilis may be induced by blood transfusion without the appearance of skin or mucous membrane lesions in the recipient—that is, without any clinical manifestations of the acute state of the disease—our methods at the present

* This assumption unquestionably holds in the cases reported by Uhlenhuth and Mulzer, and Spillman and Morell, loc. cit.

time render impossible the discovery of such cases. It is possible that the direct introduction of the virus in the blood stream, thus depriving the recipient of any possible beneficial (immunizing) effects of skin or mucous membrane inoculation, lymphatic infection and chancre formation, insures the development of an invariably active type of acute skin and mucous membrane syphilis. The observation of Brown and Pearce[9] that excision of the chancre in acute syphilis in the rabbit may result in a greater incidence of generalized lesions may have some bearing on this point, in spite of the fact that it was subsequently shown by Chesney[10] that this does not always hold true. In this connection it is also noteworthy that the intravenous injection of virus in experimental syphilis leads to the development of malignant bone lesions. These lesions are far greater in extent and severity than the bone lesions developing in the course of an experimental infection in rabbits engendered by intratesticular or intradermal inoculation.[11]

Summary. From the literature 15 cases of syphilis induced by blood transfusion have been collected and to these an additional case has been added.

An analysis of this material reveals that in every instance the disease made itself apparent in the recipient by the development of the generalized skin or mucous membrane lesions of acute syphilis. We have encountered in the literature no instance in which syphilis was acquired by blood transfusion without the development of these acute, secondary lesions.

The incubation period between the time of transfusion and the first appearance of secondary lesions has varied in the reported cases from 4 to 14 weeks.

The stage of syphilitic infection present in the donors could be determined in 11 of the 17 case reports. One donor was in the incubation stage of acute syphilis and gave blood 4 days before the appearance of the chancre; 9 had either primary or secondary syphilis at the time blood was drawn for transfusion. In the remaining instance the donor was infected by an interchange of cannulæ while giving blood in a case of postpartum hemorrhage in a syphilitic woman. Not a single instance of incontestable "transfusion syphilis" has been reported in which the disease was transmitted by blood from a donor with latent or chronic syphilis uninfluenced by pregnancy. In repeated instances donors with chronic syphilis have failed to transmit the disease.

The above observations have been shown to be consistent with our knowledge of the pathogenesis of the experimental and human disease.

Conclusion. 1. The transmission of syphilis by blood transfusion in the reported cases in the literature has been manifested in the recipient by the development of the acute secondary stage of the disease within from 1 to $3\frac{1}{2}$ months after the transfusion. Our

present knowledge does not allow of a diagnosis of "transfusion syphilis" in the absence of such developments in the recipient.

2. Syphilis is obviously transmissible by blood transfusion when, and only when, the virus is present in the donor's blood. Spirochetemia is known to occur only during the early stages of the infection before the development of latency, or during pregnancy in the chronic disease. Our present knowledge does not allow of a diagnosis of "transfusion syphilis" in the absence of these stages of syphilitic infection in the donor.

BIBLIOGRAPHY.

1. Bernheim, B. M.: Transfusion, Hæmorrhage and the Anemias, J. B. Lippincott Company, Philadelphia, p. 62, 1917.
2. Brown, W. H., and Pearce, L.: Am. J. Syphilis, **5**, 1, 1921.
3. Eberson, F., and Engman, M. F.: J. Am. Med. Assn., **76**, 160, 1931.
4. Uhlenhuth, P., and Mulzer, P.: Berlin. klin. Wchnschr., **49**, 152, 1912.
5. Moore, J. E.: The Modern Treatment of Syphilis, Charles C Thomas, Baltimore, p. 9, 1933.
6. Tzanck, A., and Werth, R.: Bull. et mem. Soc. méd. d. hôp. de Paris, **54**, 132, 1930.
7. Fribourg-Bloc: Discussion of paper by Pinard and Roberts, Bull. et mem. Soc. méd. d. hôp. de Paris, **48**, 217, 1932.
8. McNamara, W. L.: Am. J. Syphilis, **9**, 470, 1925.
9. Brown, W. H., and Pearce, L.: Arch. Dermat. and Syph., **3**, 254, 1921.
10. Chesney, A. M.: J. Exp. Med., **38**, 627, 1923.
11. Chesney, A. M.: (Personal communication).

THE EARLY RESPONSE TO VENESECTION WITH OBSERVATIONS ON SO-CALLED BLOODLESS VENESECTION.

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Venous pressure is recognized as often elevated in cardiac failure, particularly in the congestive type (Frey,[8] Gaertner,[10] Hooker and Eyster,[13] Clark,[3] Eyster and Middleton,[5] Villaret, Saint Girons and Besançon,[15] Pogany,[14] and others). This has led a number of observers to suggest that venous hypertension be considered an early sign of impending or of existing cardiac failure, and that in such instances venesection might be of great value by reducing the excessive venous load with which the failing heart must contend (Eyster[4]).

The fact has apparently been overlooked that venous pressure and "venous load" are not necessarily the same, nor are they parallel

in all instances. Cases of severe cardiac failure are on record in which venous pressure was not elevated (Villaret, Saint Girons and Besançon,[15] Pogany,[14] Arnoldi,[1] Fuchs,[9] Harris[11]), and lesions of the tricuspid valve without heart failure are said to be associated with venous hypertension (Pogany[14]). Failures encountered after venesection may be due (1) to the fact that eventually the myocardium is no longer capable of favorable response, or (2) the possibility that the venous hypertension is essential for effective cardiac function. Even in the experimental animal it has been shown that improvement does not always follow venesection when the heart is overdistended (Brams and Katz[2]).

Our experiments were planned to study the early effects of clinical venesection on pulse rate, venous pressure, and on systolic and diastolic arterial pressures in patients with varying degrees of cardiac failure. An attempt was made also to study the same features after so-called "bloodless venesection" in the same patients, in order to compare the value of this procedure with ordinary bloodletting. It was also our purpose to determine the speed of inherent readjustment to venesection, in order to observe how soon and to what degree the effects of this procedure become nullified. These experiments for the study of venous pressure necessitated the employment of an accurate method which could be used for continuous observation over a prolonged period of time. This was accomplished by the use of the principle advocated by Moritz and v. Tabora, employing sodium citrate solution with frequent flushings of the tubing and needle. The apparatus was kept in faultless working condition for over 2 hours, without discomfort to the patient and without loss of accuracy in the readings.

A series of 15 patients was studied. Congestive cardiac failure was severe in 12 of these and moderate in the remaining 3. The clinical diagnoses were hypertensive heart disease, recent coronary occlusion, syphilitic aortitis, coronary sclerosis, and cor pulmonale. All patients were definitely dyspneic and showed varying engorgement of the cervical veins. Eleven showed definite venous hypertension during the control period, the lowest reading in this group being 14 cm. of water. Three had normal venous pressure and 1 showed a venous pressure of 1.9 cm. of water. We regarded the last as an instance of venous hypotension, having adopted a level between 5 and 10 cm. of water as the normal. Systolic and diastolic blood pressures by the usual auscultatory method, and the venous pressures and heart rates were determined under the basal conditions described by Eyster,[4] *viz.*, absolute bed rest for not less than an hour. The arm was abducted from the body in order to avoid the possibility of compression of the veins and resulting interference with the venous flow from the extremity. The needle and tubing were kept patent by using sterile sodium citrate solution and by frequent flushings of the system. Patency of the needle was tested

before and after each venous pressure reading. Observations of arterial and venous pressures and pulse rates were made at 5-minute intervals during a control period of 30 minutes, and at similar intervals for 1 hour after venesection was completed. Similar observations were made in patients subjected to "bloodless venesection" before and after the tourniquets were applied. Venesection was performed by inserting a large hollow needle in the cubital vein of the arm, the quantity of blood thus removed varying from 300 to 800 cc. "Bloodless venesection" was performed by applying tourniquets on each thigh and on one arm close to the trunk, sufficient

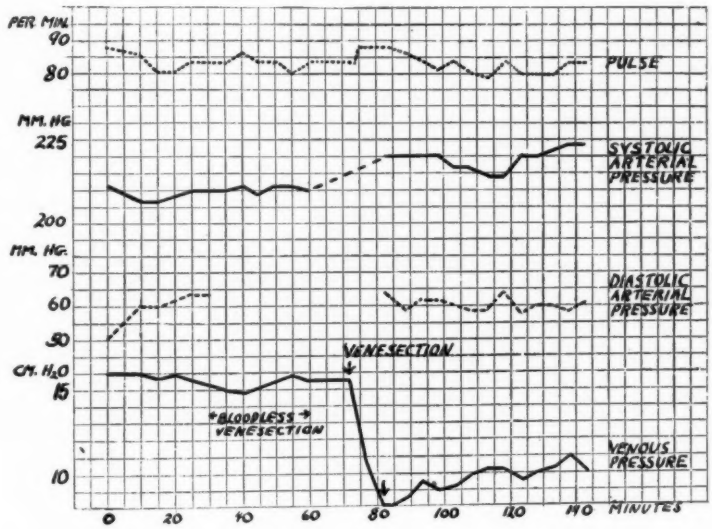

FIG. 1.—Illustrating effects of venesection on pulse rate, systolic and diastolic arterial pressure and venous pressure in Case 6, hypertensive myocardial disease with failure. "Bloodless venesection," shown by arrows, produced practically no change. Removal of 600 cc. blood, between arrows, resulted in an immediate drop in venous pressure with a slight tendency to return toward the control level later. This was associated with a practically unaltered rate, and systolic and diastolic arterial pressure levels.

compression being used to obstruct the veins without interrupting the arterial supply to the parts, as shown by persistence of the palpable pulse beyond the site of obstruction.

Ordinary blood-letting caused no appreciable change in pulse rate in any instance of this series. Similar negative results were observed after so-called "bloodless venesection" was performed.

In only 4 instances did systolic blood pressure fall appreciably immediately after blood-letting was completed, the fall in these patients varying from 19 to 26 mm. of mercury. In 3 of these, systolic pressure returned approximately to the control level within

an hour after venesection. In 4 instances diastolic pressure also fell appreciably immediately after venesection, the drop varying from 15 to 22 mm. of mercury, but here too there was a return in 2 instances to the previous level within an hour. Control systolic pressure was above 160 mm. of mercury in 7 instances, 5 of which showed readings above 200 mm. In these 7 cases of arterial hypertension there was only 1 in which venesection was followed by an appreciable immediate fall in systolic pressure, namely from 238 mm. to 212 mm. There was practically no change in the remainder of these patients. "Bloodless venesection" failed to induce any significant change in systolic pressure. Control diastolic pressure was above 100 mm. mercury in 6 instances, and in only 1 of these did venesection cause a fall of diastolic pressure. Only minor changes occurred in the remainder. In other words, the amount of blood removed, up to 800 cc., had no apparent consistent effect on either the systolic or diastolic arterial pressure except in the few instances previously noted. It was also apparent that no definite relation existed between the degree of change in blood pressure and the degree of change of venous pressure under the conditions of these experiments.

TABLE 1.—CHANGES IN VENOUS PRESSURE AFTER VENESECTION.

Experiment No.	Control venous pressure (cm. citrate sol.).	Quantity of blood removed (cc.).	Immediate drop (cm. citrate sol.).	Drop below control level 1 hour after venesection (cm. citrate sol.).
1	23.7	800	12.0 (50.6%)	6.9 (29.1%)
2	23.0	800	9.7 (42.2%)	9.3 (40.4%)
3	19.0	800	8.7 (45.8%)	13.0 (68.4%)
4	18.3	800	7.3 (39.9%)	2.3 (12.6%)
5	7.3	650	2.0 (27.4%)	1.8 (24.7%)
6	15.5	600	7.5 (48.4%)	6.5 (41.9%)
7	4.7	600	2.2 (46.8%)	1.5 (31.9%)
8	18.5	600	9.0 (48.6%)	7.0 (37.8%)
9	6.0	500	2.5 (41.7%)	1.5 (25.0%)
10	16.3	400	6.2 (38.0%)	2.0 (12.3%)
11	1.9	400	1.4 (73.7%)	1.5 (78.9%)
12	22.0	300	3.0 (13.6%)	10.0 (45.4%)
13	14.0	300	9.0 (64.3%)	2.0 (14.3%)

It will be noted that although the drop in venous pressure was greatest where the greatest quantity of blood was removed, it so happened that the pressure level returned nearer to normal in all but one of those cases where 500 cc. or less had been removed.

The removal of blood was followed by more consistent changes in venous pressure. Table 1 represents the changes observed immediately after completion of venesection and at a period 1 hour later. It will be observed that a fall in venous pressure occurred in every instance and that the control level was not reached again during the following hour, although a partial return was noted in 8 instances. The greatest initial drop occurred in those patients who had venous hypertension before venesection, the quantity of blood removed

playing a comparatively lesser rôle. The maximum fall occurred immediately after completion of venesection in all but 2 instances, and in 8 instances the venous pressure began to rise within a few minutes. No relation could be determined between the degree of fall in venous pressure and the height of control arterial pressure. There was no real effect after "bloodless venesection," venous presure showing little change for a period of 30 minutes following application of the tourniquets. At most a slight fall or rise occurred, the maximum change in either direction not exceeding 2 cm. of water.

COMMENT. The results of these experiments indicate that the theoretical value of so-called "bloodless venesection" has no basis in fact, these findings being in accord with the observations of Fuchs.[9] No important modifications in arterial or venous pressure or pulse rate were observed in our own experiments. In some instances it was noted that the discomfort induced by the tourniquets resulted in a moderate rise in venous pressure which was not followed by a fall. Ordinary venesection in the same patient always produced some fall in venous pressure, even when the smaller quantities of blood were removed. These observations suggest that so-called bloodless venesection, as performed in these experiments, is of little value in reducing venous pressure or in modifying the pulse rate or arterial pressure in cardiac failure. We could obstruct only 3 limbs because it was necessary to use one arm for estimation of venous pressure, but it is doubtful if the results would have been different had all four extremities been obstructed.

The absence of change in pulse rate, even when as much as 800 cc. of blood was removed, suggests the probability that adjustments to the loss of such quantities of blood are easily attained. We believe that the beneficial effects of venesection are due in only a small part to change in pulse rate.

The changes in blood pressure observed in these experiments were neither uniform nor striking. There were only a few instances in which blood pressure fell after venesection, even when as much as 800 cc. of blood was removed. The same was true where arterial or venous pressures were excessively high before venesection. The prompt return within an hour toward the control level of both systolic and diastolic pressures, in all but 2 instances, again demonstrates the futility of venesection as a reliable method of permanently reducing arterial blood pressure. This is probably due to the many adjustments available to keep the arterial pressure constant, which would operate to modify the effects of venesection. The fact that arterial pressure varied only slightly in patients who showed definite and consistent changes in venous pressure after venesection, reëmphasizes the independence of control of arterial and venous circulation.

Changes in venous pressure after venesection were more consistent and more marked. A fall occurred promptly in every instance

regardless of the quantity removed, but this fall was generally more marked after removal of larger quantities of blood. The drop was most marked where venous hypertension existed before venesection, but even here, as in the majority of the experiments, a partial return toward the previous level occurred within a few minutes. This observation agrees with that of Eyster and Middleton,[5,7] who also found that the drop in venous pressure was more sustained and more marked in cases of venous hypertension. Our results also show the comparative sluggishness of compensatory adjustment in the venous system. The majority of the patients stated that they felt improved after venesection, but such results must be interpreted with caution, as it is probable that genuine improvement depends on more than mere reduction in venous pressure. For example, Hitzenberger[12] found that venesection was followed by increased oxygen and decreased carbon dioxid content of the arterial blood, nor is it known how the blood reservoirs and other regulatory adjustments react after clinical venesection and we are not certain whether the "load" which the heart must pump is actually reduced after such adjustments take place. We do not wish to minimize the value of venesection in selected cases, but it is apparent that much study will be required to evaluate other factors such as circulating blood volume and minute volume output of the heart in order to determine the beneficial effects of blood letting.

RÉSUMÉ. 1. So-called "bloodless venesection" failed to reduce venous pressure or to modify pulse rate or arterial pressure in patients with cardiac failure. These results are in contrast to the changes observed in the same patients after blood letting.

2. The effects of ordinary venesection were studied in patients with cardiac failure. Observations were made every 5 minutes for a period of 1 hour after venesection was completed.

3. It was exceptional for either the systolic or diastolic arterial pressure to show an appreciable fall after venesection or during the period of observation. The same results were observed in patients with arterial hypertension as in those with normal pressure.

4. The pulse rate remained unchanged in all experiments.

5. Venous pressure fell consistently after blood letting, the maximum drop occurring immediately after completion of venesection. The fall began early in the course of venesection, becoming apparent after removal of the first 100 cc. of blood and continuing to drop as more blood was withdrawn. A partial return toward the control level within a few minutes was observed in the majority of instances, but the level of venous pressure after an hour was usually lower than the control level.

6. The fall in venous pressure was especially marked where venous hypertension existed and the actual drop also depended greatly on the quantity of blood removed. The greatest drop usually occurred where from 600 to 800 cc. of blood were removed in

cases of venous hypertension, though it so happened that a level that was nearer to normal was reached in the cases with a smaller blood removal.

7. The practical significance of the fall in venous pressure after venesection, in relation to cardiac failure, is briefly discussed.

REFERENCES.

1. Arnoldi, W.: Deutsch. med. Wchnschr., **46**, 4, 1106, 1920.
2. Brams, W., and Katz, L. N.: Am. J. Physiol., **98**, 556, 1931.
3. Clark, A.: Arch. Int. Med., **16**, 587, 1913.
4. Eyster, J. A. E.: The Clinical Aspects of Venous Pressure, The Macmillan Company, New York, 1929.
5. Eyster, J. A. E., and Middleton, W. S.: Arch. Int. Med., **34**, 228, 1924.
6. Eyster, J. A. E.: Physiol. Rev., **6**, 281, 1926.
7. Eyster, J. A. E., and Middleton, W. S.: Am. J. Physiol., **68**, 581, 1924.
8. Frey, A.: Deutsch. Arch. f. klin. Med., **73**, 511, 1902.
9. Fuchs, L.: Ibid., **135**, 68, 1921.
10. Gaertner, G.: Münch. med. Wchnschr., **50**, 2038, 1903.
11. Harris, I.: Edinburgh Med. J., **35**, 630, 1928.
12. Hitzenberger, K.: Wien. klin. Wchnschr., **47**, 1009, 1934.
13. Hooker, D. R., and Eyster, J. A. E.: Johns Hopkins Hosp. Bull., **19**, 274, 1908.
14. Pogany, J.: Ergebn. d. inn. Med. u. Kinderh., **4**, 257, 1931.
15. Villaret, M., Saint Girons, F., and Besançon, J.: La pression veineuse périphérique, Masson et Cie, Paris, 1930.

PAIN IN THROMBO-ANGIITIS OBLITERANS: A CLINICAL STUDY OF 100 CONSECUTIVE CASES.

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Pain is the most frequent symptom that leads a patient to consult a physician. Pain was the initial complaint in 90 of 100 consecutive cases of thrombo-angiitis obliterans. This study was undertaken in an endeavor to ascertain, classify, and describe the types of pain and the frequency of their occurrence in these cases of thrombo-angiitis obliterans, and to suggest, when possible, the mechanism by which such pain is produced.

In any study such as this it is well to emphasize that there are marked individual differences in the ability of the patient to feel pain, and that the threshold of sensitivity varies in the same person at different times. This has been emphasized by Libman.

A brief review of the innervation of bloodvessels seems pertinent to this discussion. The vessels of the extremities, according to Woollard, are supplied by vasomotor nerves in two ways, proximally from a continuation of the sympathetic plexuses about the aorta, and distally by branches from adjacent, mixed nerve trunks. In both instances the fibers are non-medullated, sympathetic postganglionic fibers. Peripherally, bloodvessels

receive a second type of innervation, namely, medullated or sensory fibers from proximal mixed nerves. These end in the adventitia and in surrounding tissue. The vessels in more distal parts of the extremities receive more branches from adjacent nerves than those situated proximally. On the basis of these facts it should follow that trauma to smaller vessels is more likely to cause pain than trauma to larger vessels. Two different pathways for the afferent conduction of such pain, one to nearby sensory roots, and the other up the sympathetic chain of ganglions, is the theory held by Foerster. The exact anatomic pathways are not known. Probably they are components of the thoracic spinal roots; to what extent they traverse the sympathetic trunks has not been determined. Odermatt found that sensory nerve endings are most abundant in the adventitia of the vessels, or on the surface of the media muscularis.

Types of Pain in Occlusive Vascular Disease. Pain in occlusive vascular disease may be the result of one or more of three factors: (1) that arising from the bloodvessels themselves, (2) that attributable to ischemia of tissue, including nerves, and (3) that attributable to infection.

Pain Arising from the Bloodvessels. This type of pain may be caused by spasm, stretching, or inflammation. Arterial pain is a characteristically constant, burning, gnawing pain, tending to spread out without reference to nerves. Barium chlorid, injected into arteries, causes a spasm of the smooth muscle, resulting in severe pain (Fröhlich and Meyer). We have observed prolonged spasm of the brachial artery, following perivascular neurectomy, which initiated a dull aching pain of the forearm and hand. There was no profound spasm of the smaller vessels, as shown by the color of the hand. Severe pain is rarely observed in the ischemic attacks in Raynaud's disease; the usual sensation is a dull, numb feeling. In operations under local anesthesia it has been noted that clamping or pulling an artery may give rise to pain. Bazett and McGlone demonstrated that simple arterial puncture caused a dull, aching, sickening pain which was diffuse in character, and was often referred to regions distal to the site of puncture. We have observed that puncture of smaller arteries is accompanied by more intense pain than puncture of larger arteries. Waterston reported similar observations. Odermatt was of the opinion that pain from injection of an irritating solution into an artery was produced in the finer arterial branches where the solution could penetrate the wall of the vessel and come in contact with sensory nerve endings. The endothelium of the vessel seemed to be insensitive to pain. He also demonstrated that pain may be elicited by distention of arteries, regardless of their caliber. The injection of solutions of sodium iodid into the femoral artery causes so much pain that general anesthesia may be required. Moore and Moore concluded that this pain was not the result of stretching of the vessel or contraction of its wall, but was produced in the finer arterial branches.

Pain Attributable to Ischemia of Tissues. Such pain is probably the result of ischemia of nerves. Ischemic neuritis is a misnomer,

as the lesion is one of degeneration from lack of adequate blood supply rather than of inflammation. Infiltration of nerve sheaths by an inflammatory process is a mild and late affair. In contracting muscle in which there is an inadequate supply of arterial blood, incompletely metabolized substances are believed to act as irritants to nerves, producing the characteristic symptom of claudication.

Infection as a Cause of Pain. Pain resulting from infection does not need elaboration here. It is important to realize that infection in tissue incompletely supplied with oxygen takes on different characteristics than in tissues with a normal supply of blood; local heat is absent and intensity of pain is heightened.

In view of these observations it is not surprising that pain should be an outstanding and early symptom of thrombo-angiitis obliterans, since the pathologic processes involve occlusion of major and minor arteries and veins, inflammation of vessels, skin, and muscle, ischemia of nerves, muscle, and skin, secondary, infectious, trophic changes in the skin, and vasospastic disturbances.

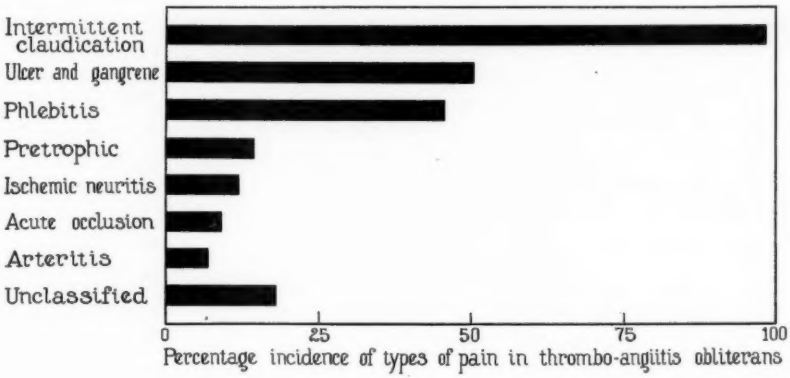

FIG. 1

Pain Induced by Exercise and "Rest" Pain. In this series of 100 consecutive cases of thrombo-angiitis obliterans two major groupings of pain were noted: (1) pain brought on by exercise, such as that of intermittent claudication and phlebitis, and (2) pain occurring during rest. Rest pain was further classified as pretrophic and trophic, the latter resulting from ulcers or gangrene; inflammatory, such as from arteritis or phlebitis; that due to acute occlusion with massive ischemia; that of ischemic neuritis; vasospastic, and unclassified. The incidence of these various types of pain is given in Fig. 1.

Intermittent Claudication. *Pain Related to Exercise.* Intermittent claudication occurred in 98 of the 100 cases, marking the onset of symptoms of the disease in 75 (Table 1). The most frequent

sites of pain were the arch of the foot and the calf of the leg; it may occur, however, in any of the muscles of the extremity, in the toes, thigh, forearm, hand, or fingers. The pain which is induced by exercise is initiated with a feeling of dull aching fatigue, or sense of constriction in the affected muscles. If exercise is continued, a severe cramping pain develops which necessitates cessation of activity. Sensations of coldness and numbness may accompany the pain, or, in some cases, a sensation of burning. One patient described claudication as a feeling of tightness which persisted and increased in severity for a few seconds after he stopped walking, and then seemed to "flow away." The amount of exercise sufficient to produce claudication varies from walking a few yards to a mile or more, but in a given case it is remarkably constant. Repetition of a standard exercise test (120 steps per minute) in a group of patients revealed a variation in time of less than 10%. Nervousness, emotion, weather, and fatigue modify the time of onset of claudication in some subjects. In 4 cases the severity of claudication was increased by cold weather, in 1 by hot weather. The pain is relieved by a rest of from a few seconds to 10 minutes. After a period of rest the original exercise can usually be repeated. Fast walking will bring on claudication at a shorter distance than will slow walking. Walking uphill initiates the pain of claudication more rapidly than walking on level ground. As the occlusive process progresses proximally, claudication may progress from arch to calf to thigh, with a gradually diminishing walking distance. The progression of the disease may be vividly demonstrated by the decreasing tolerance to exercise.

TABLE 1.—INTERMITTENT CLAUDICATION IN 98 CASES OF THROMBOANGIITIS OBLITERANS.

Site of pain.	Right	Left.	Bilateral.	Time of onset.	Cases.	Status of claudication.	Cases.
Arch and foot	4	5	15	First symptom of disease	75	Progressive	38
Calf . . .	5	6	29	Less than 1 year after onset	10	Stationary	18
Arch and calf	8	8	16	1 to 3 years after onset	6	Improving	14
Thigh . .	5	1	3	3 to 5 years after onset	3	Progressive, then improving	7
Palm and forearm	2	1	0	More than 5 years after onset	4	Unknown	21

The pain of claudication apparently is the result of some chemical substance formed during muscular contraction when the blood

supply is deficient. Roth has shown that the lactic acid of the veins of the affected extremity increases sharply after exercise in cases of occlusive disease of the arteries; an exact parallelism of the concentration of lactic acid with the intensity of the pain, however, is not demonstrated. The relationship of level of closure of arteries to the situation of the pain of claudication is important. It may be stated as a general rule that claudication in the muscles of the calf indicates occlusion of the popliteal arteries; if pain is limited to the feet, the dorsalis pedis and posterior tibial arteries are occluded. In 72 cases in which claudication in the muscles of the calf occurred, the popliteal vessels were graded 0 in 53, reduced in 10 (indicating pulsations palpable in collateral arteries), and graded 4 (normal) in 9. The probable explanation of claudication in these 9 cases is that the popliteal arteries were occluded at their bifurcation, although they pulsated normally in the region palpated. Conversely, a few patients with occluded popliteal arteries do not have claudication in the muscles of the calf. This could readily be explained on the basis of an exceptionally well-developed collateral circulation. In cases in which there is pain of claudication in the thigh, the femoral or iliac arteries are occluded.

The other type of pain that is induced by exercise occurs in certain cases of phlebitis, and it will be discussed in connection with that subject.

TABLE 2.—REST PAIN IN THROMBO-ANGIITIS OBLITERANS.

Time of onset of pain.	Pre-trophic.	Ulcer.	Gan-grene.	Phlebitis.	Arteri-tis.	Acute occlu-sion.	Ischemic neuritis.
At onset of disease	3	2	0	15	4	3	..
Within first year	1	7	4	14	1	1	2
1 to 3 years later	5	14	8	7	1	2	6
3 to 5 years later	3	9	3	4	..	1	1
More than 5 years later	1	6	5	4	..	..	2
More than 10 years later	1	5	3	2	2	2	1
Severity of pain:							
Grade 1 (mild)	1	4	1	10	2	4	2
Grade 2	3	5	3	2	..	..	2
Grade 3	2	21	9	3	1	5	4
Grade 4 (severe)	..	2	4	0	..	..	3
Tenderness only	..	..	..	15	1	..	..

Pain Occurring with Rest. *Pretrophic Pain.* Fourteen patients complained of rest pain which we have designated "pretrophic." This term is used because ulcers or gangrene frequently developed at the site of pain from a week to 6 months after its onset. Six cases are included under this heading in which trophic lesions failed to develop; we feel justified in thus classifying them, as the pain was of the same character, and often accompanied lesions on neighboring digits. This type of pain is well localized in the digits or in adjacent regions; it is described as a burning, gnawing type of pain, usually continuous and worse at night, or as an aching sensation

associated with local tenderness. In 2 cases it was intermittent in character. Four patients obtained relief on keeping the affected parts in a dependent position and 1 from walking; in 1 case exercise increased the discomfort. The time of onset of the pain in relation to the beginning of the disease and its severity are given in Table 2. The microscopic picture of the skin in these cases reveals a marked increase in fibrous tissue in the deeper layers (Figs. 2 and 3). This tissue contracts about the terminal nerve fibers causing irritation and ischemia, and is probably responsible for the pain. Another possible cause of pain is a small infarct, with inflammation of low grade eventuating in necrosis.

Pain of Ulcers and Gangrene. Ulcers or gangrene of one or more digits, with pain, developed in 50% of the cases studied. There were 17 patients who had both gangrene and ulcers, 26 with ulcers alone, and 7 with gangrene without ulceration. Ulcers were multiple in 25 cases, single in 18. A solitary area of gangrene was noted in 13 cases, multiple areas of gangrene in 11. The onset of pain with these trophic lesions was gradual, the severity increasing as the ulcers or gangrene progressed. The pain was described as burning, stinging, or tingling and was localized in the region of the lesion. It was usually continuous; in a few cases, however, it was paroxysmal. Some patients used the adjectives, "deep," "grinding," "driving," and "aching" to describe it. Projection of the pain was rarely observed. Marked hyperesthesia about the lesion was frequent. In 24 cases the pain was more severe at night, and in 18 relief on dependency was an important feature. These patients often slept sitting in a chair, or with the foot hanging over the side of the bed. External heat, by means of a baker, often aggravates the pain. Gangrene occasionally develops without any pain. This occurred in 1 case in this series.

Trophic pain was relatively rare in the first year of thromboangiitis obliterans (Table 2), and not infrequently occurred 5 and 10 years after the probable onset of the disease. It was often severe, the intensity being graded 3 or 4. The chronicity of pain resulting from ulcer is worthy of emphasis; it often lasts for months. The primary cause of this type of pain is probably secondary infection or localized edema. Slow healing is characteristic, owing to the ischemic state of the tissues. It is difficult to explain why dependency should give relief from pain. We have noted that the temperature of the skin is not consistently or significantly raised while the extremity is in this position. Elevated venous pressure, creating stasis of blood in the extremity, possibly is a factor.

Nocturnal exacerbation is characteristic of many types of distress. In explaining this one must consider that there are no external factors to divert the attention of the patient from his pain, and it thus occupies a central position in his mind. Possibly also the

lowering of metabolic processes and of systemic blood pressure play a part in increasing ischemia.

Pain of Inflammatory Lesions of the Bloodvessels. Localized inflammatory lesions, namely, phlebitis and arteritis, occurred in 46 and 7% of the cases, respectively. In 18 cases there was but one attack of phlebitis; in 11 cases two attacks, and in 16 phlebitis occurred on a number of occasions, at times being almost continuous. Phlebitis was superficial in 44 cases, deep in 2, and both superficial and deep in 2 others. It was the first symptom of the disease in 15 cases, and often occurred early in its course (Table 2). When phlebitis occurs in the feet, pain on standing or walking is induced. Pressure on and movement of inflamed tissues cause the pain, which does not simulate the distress of claudication resulting from a given amount of exercise.

Case Report. A man, aged 29, of Dutch ancestry, was first seen at the Clinic February 4, 1929. Six months previously, red tender nodules had developed along the course of the veins of the right calf. There was associated muscular soreness and stiffness. Phlebitis migrated from one region to another in the right leg and foot for a period of 6 months. About the same time the patient noted soreness in the right instep, induced by walking a few blocks, which was relieved by rest. At the time of examination the right dorsalis pedis and posterior tibial arteries were occluded, whereas those of the left foot evidenced reduced pulsations, graded 2 to 3.

The patient was seen again in 1933, having had another bout of phlebitis in both legs and arms in October, 1930, with local, burning discomfort. There had been similar recurrences at yearly intervals. When the lesions were in the feet, pain was a prominent feature. Arterial occlusion had been progressive in both legs, closing both popliteal arteries. There was claudication involving the muscles of the calf, with sharp reduction in the amount of walking the patient could do.

These episodes of phlebitis, flaring up at yearly intervals, revealed the relapsing nature of the disease. Thrombosis of the arteries seemed to parallel the phlebitis. The pain of phlebitis was disagreeable and annoying, but there were no residual symptoms when the condition was quiescent, as compared to the arterial closure that left a progressive impairment of walking.

The pain resulting from an inflammatory lesion of the vein is generally minimal. In 15 cases there was only tenderness along the course of the vein. Pain of grade 4 did not occur, and that of grade 3 occurred in only 3 cases. In cases of phlebitis, when pain was an important feature it was of a dull, aching or burning type, fairly well localized, and was at times associated with muscular soreness, stiffness, and twitching. Four patients had exacerbations of the pain with exercise, 1 of them suffering a sharp, stabbing pain that was projected peripherally with activity of the involved part that suggested periadventitial neuritis.

The pain of arteritis was only slightly more severe than that of phlebitis. It marked the onset of thrombo-angiitis obliterans in 4 cases. A tender, nodular swelling, progressing along the course of the artery, which became enlarged and pulseless, was the primary

feature. There was a generalized aching pain with coldness peripheral to the involved arterial segment. The radial, ulnar, and brachial arteries were the arteries involved in all but 1 case, in which painful arteritis of the lower femoral and popliteal arteries was present. One patient complained of cramping of the forearm and hand lasting a week; another complained of a constant, frozen, gnawing sensation, which was relieved by exercise. In 1 case of radial arteritis there was a burning, spasmodic, agonizing pain, referred to the thumb and index finger. In this case the adjacent peripheral nerve may have been involved in the inflammatory process. With the abundant nerve supply in the adventitia, it is not difficult to explain pain resulting from arterial inflammation. The surprising feature is that the pain of arteritis is so mild and is present so infrequently, as arteritis is probably present in all cases of thrombo-angiitis obliterans, although it produced symptoms in not more than 7% of our cases. The intensity and situation of the inflammatory process probably determines the presence or absence of pain. Clinical observation indicates that phlebitis of the large veins is usually less painful than phlebitis of superficial vessels, with involvement of superficial tissues. The relative infrequency of pain in the more deeply situated arteries may be explained on a similar basis.

Acute Occlusion. The pain of acute occlusion of a large artery is of sudden onset, with tenderness at the site of occlusion and generalized pain which is projected peripherally. There is often severe, cramping pain in the muscles. The extremity is cold, numb, cyanotic and at times swollen. The pain is usually of short duration, lasting from a few hours to several days, with gradual diminution in intensity. Movement and pressure may increase the pain, and there is often nocturnal exacerbation. The muscles are tender and the skin hyperesthetic and intermittently cyanotic, a vasospastic expression of an acute ischemic neuritis. The pain is the result of ischemia of mixed nerves and severe vasospasm. In only the most severe cases are there objective neurologic signs of neuritis. The short duration of the pain may be explained by the rapid increase of collateral circulation. This has been followed by studies of temperature. If thrombosis is not progressive, almost complete recovery of the surface temperature of the digits may occur in from 2 to 3 days. Residual hyperesthesia, numbness, tingling, and mild paroxysms of pain may be present for weeks.

Case Report. A man, aged 49, was seen at the Clinic in July, 1933. In September, 1931, he had suddenly experienced a moderately severe pain in the left foot and in the muscles of the calf of that leg. The left first toe and ball of the foot had been numb, and the entire lower portion of the left leg cold and cyanotic. The pain had lasted only a few days. Shortly after this, a superficial phlebitis had appeared about the right external malleolus. Since 1931 the patient had had pain in both calves after walking from one to three blocks; the pain had occurred sooner after fast walking or after walking uphill. Examination at the time of admission revealed absence of pulsations in both popliteal and distal arteries.

The first symptom of thrombo-angiitis obliterans in this case was sudden occlusion of the left popliteal artery. From then on the episodes of phlebitis and distress of claudication indicated the nature of the process. Sudden occlusion initiates the onset of thrombo-angiitis obliterans in about 10% of cases.

Ischemic Neuritis. Ischemic neuritis occurs relatively late in the course of thrombo-angiitis obliterans, only 3 cases having been observed in the first 18 months of the disease. Among 12% of the patients in this series this lesion developed; in 2 cases both lower extremities were involved. The neuritis was severe in 7 cases, mild in 5. The pain, in cases in which involvement was extensive, is severe, diffuse, covers large areas, and is spasmodic. It does not correspond to any definite distribution of nerves. There are sharp, shooting pains which extend from one end of the extremity to the other. The pains at times are pulling, tearing, and agonizing; at other times they are burning and throbbing. In addition to these paroxysms, there may be a constant, dull, diffuse pain which shifts from one region to another. During paroxysms the extremity may appear a mottled dark bluish-red owing to excessive vasoconstriction which is a result of the inclusion of sympathetic fibers in the neuritic lesion. With cessation of the severe pain, the color may become more nearly normal. The paroxysms of excruciating pain occur most often at night, and may last for several hours. Large doses of morphin and hyoscin, hypodermically, and alcohol by mouth, either singly or combined, may fail to give relief for more than a short time. Elevation of the extremity gave partial relief in 2 cases. Fever therapy had little effect. Rarely, pain has been so severe, constant, and intractable that amputation or chordotomy has been necessary.

Severe forms of ischemic neuritis ran a prolonged course (from 1 to 8 months) in this group of cases. The pain gradually diminished in severity and the area of distribution became less in extent.

Mild cases of ischemic neuritis are similar to those just described, although a smaller portion of the extremity is involved and the pain may follow a definite nerve distribution. One case of posterior tibial neuritis and 1 of superficial peroneal neuritis were present in this group.

The bloodvessels of the affected extremity are usually extensively involved. Of 11 cases of neuritis of the lower extremity, femoral pulsations were absent in 7, and reduced in 1. In the 3 patients with open femoral arteries the neuritis was confined to the lower part of the leg and foot.

Complete neurologic examination of the involved extremity was carried out in 6 cases: reflexes were reduced in 3 and normal in 3. There were sensory changes of marked degree in 1 case, slight changes in 3, and no changes at all in 2. The most frequent sensory change was marked hyperesthesia; the second, partial anesthesia

of the affected limb. Numbness and coldness, tingling, and other forms of paresthesia, with varying degrees of pain were the usual symptoms.

Sympathetic ganglionectomy had little influence on the occurrence of ischemic neuritis. Three patients had undergone this operation from 1 to 3 months before neuritis developed. One patient had neuritis in one leg before, in the other after, sympathectomy. The operation caused exacerbation of an existing neuritis in 1 case and partial relief of pain in another.

The pain of ischemic neuritis we believe to be the result of degenerative changes in nerves brought about by a lack of blood supply to those nerves rather than the result of actual inflammation from contiguity of diseased vessels. Woltman and Wilder, in a study of neuritis in diabetes, concluded that atherosclerosis of the nutrient vessel to a nerve played a prominent part in the production of the neuritis. Pain, paresthesia, and areflexia, without the usual sensitivity of nerve trunks, were the most important characteristics in their group of cases. The same features were predominant in the cases described here. Priestley, in 1932, demonstrated that peripheral nerves of extremities amputated for diabetic gangrene gave evidence of wallerian degeneration and fibrosis, the changes being more prominent distally and being proportional to the arteriosclerotic changes in the vessels. He suggested that the peripheral origin of the degeneration made it probable that it was dependent on ischemia. Brown, Allen and Mahorner found evidences of inflammation in nerve trunks in several cases of thrombo-angiitis obliterans. This was not the usual change in cases of ischemic neuritis.

Figures 4 and 5, from a case of thrombo-angiitis obliterans with advanced ischemic neuritis, reveal many nerve bundles with a marked loss of myelin and evidences of degeneration, whereas there is almost no evidence of inflammation or of fibrosis about the nerve. As in the reports just referred to, ischemia in this case seems to be the important factor in the production of the neuritis.

The paroxysmal character of the pain in this condition may be partly explained on the basis of vascular spasm that causes additional ischemia, since during the paroxysms the extremity is often more cold, cyanotic, and mottled than at other times. Exact parallelism of pain and changes in temperature could not be demonstrated in 1 case.

Case Report. A man, aged 48, American, had had his first symptoms of arterial disease in 1930 when arteritis of the right brachial artery had developed, causing cramping pains in the right forearm and hand. A nodule could be palpated in the brachial artery. Following this he had noted cramping and coldness of the hand with exercise. In 1931, intermittent claudication of the left arch and calf had developed after he had walked one block. In October, 1932, he had had acute occlusion of the right femoral artery, in Hunter's canal, with severe pain throughout the entire right leg; this pain had lasted several days and had prevented sleep. A few weeks

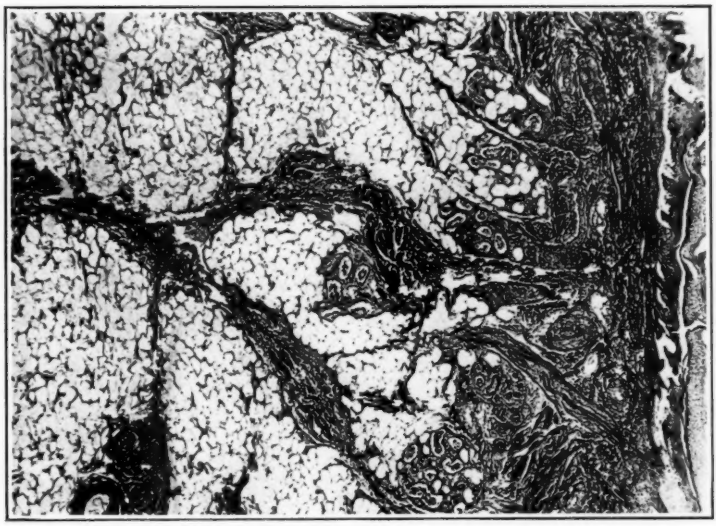

FIG. 2.—Normal skin of a digit (× 30).

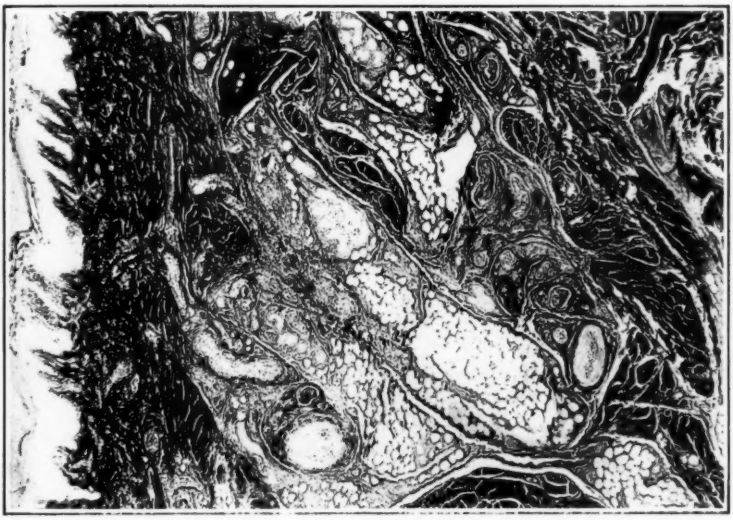

FIG. 3.—Skin of digit; thrombo-angiitis obliterans with pretrophic pain. The increase in density and amount of fibrous tissue in the corium and subcutaneous tissues, with diminution of fat and without signs of inflammation, may be noted (× 30).

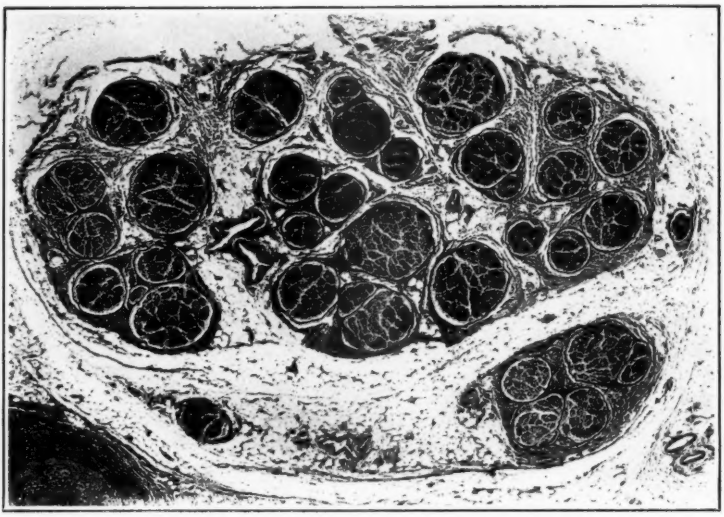

FIG. 4.—Cross section of posterior tibial nerve; ischemic neuritis in thrombo-angiitis obliterans. (Weigert's myelin sheath stain, × 15.)

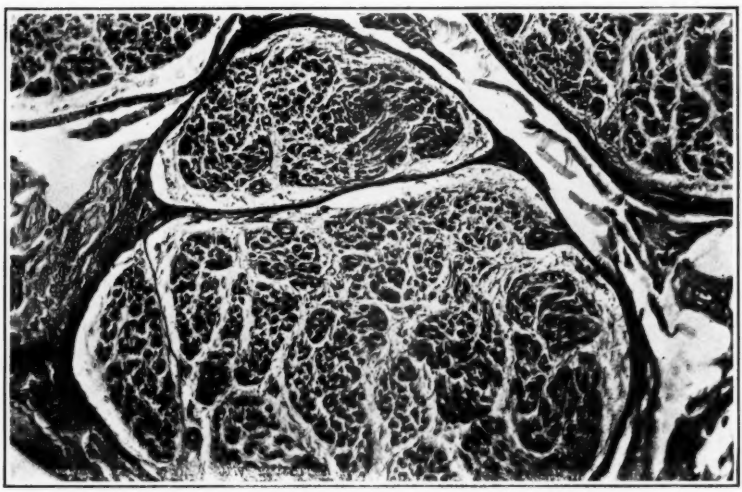

FIG. 5.—Cross section of posterior tibial nerve; ischemic neuritis in thrombo-angiitis obliterans. (Weigert's myelin sheath stain, × 115.)

after this acute occlusion, severe rest pain had appeared in the upper part of the right leg and in the calf and foot. The pain had occurred most often at night, and had lasted 1 or more hours. The pain had been exceedingly severe, of grade 4, and had required morphin in large doses for relief. In addition to these paroxysms a constant mild pain had been present in the entire extremity, with numbness of the toes, and weakness of the muscles of the leg.

On examination there was hyperesthesia of the skin, diminished sensation to pinprick, and light touch, and tenderness of the leg below the knee. The Achilles and patellar reflexes were absent in this leg. All of the arteries of the right arm, left leg, and right leg below the midthigh were completely occluded. The right leg was amputated in November, 1932, because of spreading gangrene.

In December, 1932, the patient had superficial phlebitis of the inner aspect of the left thigh; this spread below the knees. The left foot and left leg were swollen, suggesting that a deep phlebitis also was present. In the same month he noted severe burning, throbbing, spasmodic pain in the left leg, associated with a purple and white mottling of the left foot. The spasms lasted about an hour and were relieved somewhat by alcohol. The muscles of the foot were weak and the skin hypersensitive. In January, the patient had some cramp-like shooting pains in the left leg and foot, without vasospastic disorder. After about 9 weeks, he became free of pain until June, 1933, when superficial phlebitis of the stump of the right leg and of the left thigh developed; this was associated with edema of the left foot and leg. In July, 1933, the left first and third toes became gangrenous. Rest pain was severe and the leg was markedly hyperesthetic. The gangrene spread, necessitating amputation of the leg in July, 1933. The patient died, September 9, 1933, of coronary occlusion.

The severe forms of ischemic neuritis are more prone to develop with the rapidly progressive forms of thrombo-angiitis obliterans. The periods of remission are short, the lesion involves large arteries, and collateral circulation does not have time to develop adequately. These forms may be justly designated as fulminating, or malignant, types.

Vasospastic Pain. One patient noted a cramp-like pain in the muscles of the right calf, associated with a cold, white foot; the condition was relieved by nitroglycerin. Pulsations in the foot were not palpable while the pain was present but could be felt after administering a vasodilating drug. This pain seemed certainly to be of vasospastic origin, secondary to thrombo-angiitis obliterans. Usually, blanching or episodes of cyanosis, so frequently observed in this disease, do not cause pain. Sensations of numbness and aching are the usual complaints.

Other Types of Pain. Unclassified pain was found in 18 patients. The etiology in some cases could be surmised, in others the history was too vague and nonspecific to justify any inference as to the cause. In 2 cases the pain was probably the result of ischemia; the story was of aching pain, swelling, coldness and numbness of a digit, of several months' duration. Another patient complained of intermittent pain in the toe, accompanied by redness. This may have been a localized inflammatory process. Rest pain in the

calf of the leg, continuous for days, with occasional exacerbations relieved by heat, exercise, and change of position, was, conceivably, the result of localized arteritis or phlebitis.

Comment. The accessibility of the extremities for objective study has rendered the investigation of disorders of the bloodvessels particularly fascinating. The changes in pulsation in the palpable arteries allows the course of the obliterating process to be followed with great accuracy. Vasomotor disorders are obvious, exhibiting changes in color and variation in surface temperature. The evolution of trophic lesions is visible as are surface capillaries to microscopic observation. In addition to these clinical investigations, correlation with pathologic material is made possible from studies of amputated limbs or digits and of specimens at biopsy. The advent of arteriography (Allen) of the extremities by the intra-arterial injection of opaque substances, such as thorium dioxid, has made visible to an astonishing degree the distal arterial architecture, more particularly of the upper extremities. Arteriography has brought out two important factors: (1) that many male patients with disorders which were thought to be vasomotor in origin have been shown to have organic occlusion of the smaller digital arteries, and (2) that the arteries of the hands are involved in a much higher percentage of cases of thrombo-angiitis obliterans than was previously believed. It is apparent that occlusion of the arteries may occur in the face of complete absence of any signs or symptoms, indicating rapid development of collateral circulation. This is particularly true in the upper extremities.

There are two major types of pain in cases of thrombo-angiitis obliterans; (1) that resulting from ischemia of the nerves of the skin, or of the larger nerve trunks, or ischemia of the muscles, each of which causes a recognizable type of distress, and (2) that resulting from inflammation of the veins, of the arteries, or of the cutaneous tissues. This grouping holds true not only in cases of thrombo-angiitis obliterans, but also in those of other occlusive diseases of the arteries, such as arteriosclerosis, or occlusion from embolism. In arteriosclerotic disease, with the exception of that attributable to superficial phlebitis and arteritis, the same types of pain are observed as in thrombo-angiitis obliterans.

Ischemic episodes, with blanching or cyanosis of the skin, do not cause severe pain. Similar absence of significant degrees of pain occurs in Raynaud's disease, a primary vasospastic disorder. The complaint is usually a feeling of numbness or aching.

Ischemia of the larger nerve trunks causes true, ischemic degenerative changes in the nerve fibers. Actually this is not true neuritis, as only occasionally is an inflammatory process present. The pain of ischemic neuritis is fairly characteristic in that it appears with rest, occurs in the absence of trophic lesions, and usually follows sudden closure of one of the larger arteries of the limbs. The

vasospastic changes in color that accompany this are secondary manifestations of involvement of sympathetic fibers in the mixed nerve trunk.

Ischemia produces no pain in the resting muscle; pain occurs only with exercise, and this pain is known as claudication. This symptom, which comes after a constant amount of muscular activity, is thought by Lewis to be attributable to the accumulation of some "X" substance which is capable of producing pain.

Pain resulting from inflammation of the arteries and veins is not severe and is usually self-limited; it exists for a period of from 2 to 3 weeks, the time for the subsidence of the inflammatory lesion.

It is interesting to speculate as to why arteritis does not produce more serious degrees of pain. In only a small percentage of cases is arteritis painful. When present, the pain is never severe, and in the majority of cases inflammatory lesions of the arteries are unrecognizable as far as the local inflammatory process is concerned.

Pain, in older subjects with occlusive arteriosclerotic disease, is less intense, as a rule, than that observed in cases of thrombo-angiitis obliterans. Ischemic neuritis is probably of equal frequency in both arteriosclerotic disease and thrombo-angiitis obliterans. In the former, trophic lesions as a rule are less intense unless diabetes is present. With diabetes, the ulcers are usually of the moist variety, with marked degrees of secondary infection. The process, however, is primarily thrombosis resulting from arteriosclerosis. Diabetes simply modifies the type and course of the inflammation of ischemic tissues.

The individual sensitivity of the patient to painful lesions of peripheral arterial disease varies greatly, and modifies the clinical symptoms to a considerable degree. It is amazing the amount of pain a stolid individual will endure, as compared with the relatively small degrees of pain that a highly sensitive subject can tolerate. These individual differences in sensitivity are particularly important from the standpoint of treatment. Amputation or radical neurologic procedures may be imperative because of the low threshold for pain which causes a breaking of the morale of a hypersensitive person.

An interesting group of patients have been observed who have advanced grades of closure of the arteries and ulcers of the digits but with complete absence of pain. This cannot entirely be explained on the basis of lowered sensitivity of the individual to pain, and it has occurred among patients without demonstrable evidence of neuritis. Pathologic studies of the amputated extremities of these patients have thrown no light on these paradoxical findings.

Differentiation of the types of pain in cases of occlusive disease of the bloodvessels assumes importance from the standpoint of treatment. The relief of pain is a paramount problem. Often on its control depend preservation of the morale of the patient and preservation of the limbs. As recognition of the basis of the pain

has advanced, so has more effective therapy. The newer tissue extracts (Roth) used in treatment of the pain of claudication have given increased range of activity in a high percentage of cases. More effective control of the pain resulting from ulcers and gangrene has been obtained by rest, by immersion of the affected parts in mild non-irritating solutions, such as boric acid, by the use of anesthetic solutions locally, by induction of fever by foreign proteins, and occasionally by section of the sensory branches of the peripheral nerves. Sympathetic ganglionectomy is not carried out for the relief of pain, but has a definite field of usefulness in the prevention of recurrent ulcers. The pain of phlebitis and arteritis frequently can be controlled by the use of Roentgen therapy. The control of the pain of ischemic neuritis is at present a major problem. No entirely effective treatment is available. The milder forms are self-limiting and can be controlled with mild analgesic drugs, or alcohol by mouth, and treatment with Roentgen rays over the lumbar portion of the spinal column. In the severe forms of neuritis control of pain may be often impossible and operative measures may be necessary; in several cases chordotomy has been performed.

Summary. There are 7 distinct recognizable types of pain in thrombo-angiitis obliterans. The two major factors involved in the production of pain are: (1) ischemia, and (2) inflammation. The types of pain observed in arteriosclerosis obliterans are similar to those in thrombo-angiitis obliterans, with the exception that pain resulting from phlebitis and arteritis is absent.

Intermittent claudication was the initial symptom in more than 90% of the cases in this series. The recognition of the arterial basis of this symptom is of crucial importance, as avoidance of ulcers and gangrene and preservation of limbs depend largely on early appreciation of the circulatory impairment. The presence or absence of pulsations in the peripheral arteries should be determined in any case in which pain in the extremities is a prominent feature.

All types of pain present in this disease are amenable to treatment with the exception of that attributable to severe degrees of ischemic neuritis.

The decrease in the incidence of amputation in cases of thrombo-angiitis obliterans has followed, to a large degree, the effective treatment of pain.

REFERENCES.

Allen, E. V.: The Value of Arteriography, Radiology, **22**, 678, 1934.

Bazett, H. C., and McGlone, B.: Note on Pain Sensations which Accompany Deep Puncture, Brain, **51**, 18, 1928.

Brown, G. E., Allen, E. V., and Mahorner, H. R.: Thrombo-angiitis Obliterans, Philadelphia, W. B. Saunders Company, p. 219, 1928.

Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Berlin, Urban and Schwartzenberg, **8**, 360, 1927.

Fröhlich, A., and Meyer, H. H.: Zur Frage der visceralen Sensibilität, Klin. Wchnschr., **1**, 1368, 1922.

Libman, E.: Observations on Individual Sensitiveness to Pain: with Special Reference to Abdominal Disorders, J. Am. Med. Assn., **102**, 335, 1934.

Moore, R. M., and Moore, R. E.: Studies on the Pain Sensitivity of Arteries: Some Observations on Pain-sensibility of Arteries, Am. J. Physiol., **104**, 259, 1933.

Odermatt, W.: Die Schmerzempfindlichkeit der Blutgefässe und die Gefässreflexe, Beitr. z. klin. Chir., **127**, 1, 1922.

Priestley, J. B.: Histopathologic Characteristics of Peripheral Nerves in Amputated Extremities of Patients with Arteriosclerosis, J. Nerv. and Ment. Dis., **75**, 137, 1932.

Roth, G. M.: Personal Communication to Authors.

Roth, G. M., and Brown, G. E.: Effect of Tissue Extracts on Intermittent Claudication, Med. Clin. North America, **18**, 609, 1934.

Waterston, D.: On Pain, Lancet **1**, 943, 1933.

Woollard, H. H.: The Innervation of Bloodvessels, Heart, **13**, 319, 1926.

Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus : Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med., **44**, 576, 1929.

THE FOUR-LEAD ELECTROCARDIOGRAM IN CORONARY SCLEROSIS.

A Study of a Series of Consecutive Patients.*

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It is becoming more apparent that the electrocardiogram is an important element in evaluating the condition of the coronary circulation. Its place in the diagnosis of recent coronary occlusion is well established but its use in other forms of coronary insufficiency is still not fully appreciated. It is known that serial electrocardiograms over a long period of time in patients with coronary sclerosis frequently show slowly progressive changes in the conventional 3 leads, which have been ascribed to the myocardial changes resulting from the progressive coronary sclerosis.[1,2,3] Since the precordial lead has been shown to be so definite an aid in the diagnosis of recent coronary occlusion,[2,4,5,6] it seemed to us reasonable to suppose that it might also afford some information as to the progress and degree of myocardial damage resulting from coronary sclerosis. Information concerning the extent of the myocardial damage and the degree of coronary insufficiency present obtained at an early period, it seems to us, is of far greater value to the clinician than evidence as to the localization of the myocardial lesion obtained

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later after an occlusion has finally occurred. In fact, in most instances where patients with recent coronary occlusion have come to autopsy, the hearts have been found to show definite coronary sclerosis often associated with extensive myocardial fibrosis and infarcts of long standing which were thought to have contributed to the earlier clinical disability.[3] With this in view we have undertaken a study of the 4-lead electrocardiogram in a large series of patients with coronary sclerosis diagnosed clinically.

Procedure. 1. *Technique of Taking Lead IV.* The method used for taking the 4th lead was similar to that described by Wolferth and Wood.[4] This was chosen because considerable data have already been assembled with this particular method, so that it has become conventional and comparisons with previous work would, therefore, be more intelligible. The procedure established by Katz and Kissin[5] was followed with some modification. In brief, with the patient on his back, one of the standard ($2\frac{1}{2}$ by 5 cm.) tin electrodes was applied at the level of the 4th interspace, a little to the left of the sternum and attached to the right arm terminal, and the other electrode was placed on the posterior chest wall or on the left leg and attached to the left arm terminal. Care was taken to insure a close application of electrodes, to keep the skin resistance low, and to prevent overshooting. The curves obtained using the left leg as the point of lead off were similar to those using the posterior chest wall (Wolferth and Wood[4]). Wilson[7] has clearly shown that the location of the anterior precordial electrode is far more important than that of the other. We feel that it is advisable for convenience to place the posterior lead on the leg in all patients; this is our practice at present. This combination we have designated throughout this report as Lead IV. The use of the 4th interspace just to the left of the sternum was selected as the place for the electrode because it is an easily ascertainable and fixed point for use in taking serial records and for comparison among different individuals. This does not apply to the point of the maximum apex beat used by Wolferth and Wood[4] and others. The 4th interspace is over the heart, and is less influenced by the position of the diaphragm than the 5th interspace which is used by some other workers. In normal persons, records obtained with the anterior electrode in the 4th interspace show a practically constant electrocardiographic contour in successive curves.

It has been suggested that the precordial electrode be connected to the left arm terminal instead of the right. If this were done the exact inverse image of the curves here described would be obtained with the phase signs of positive and negative reversed. It would be unfortunate, in our opinion, to confuse the issue by such reversal from the established practice, particularly since the direction of deflections is purely arbitrary and the present curves have gained wide use. Unless real justification is given for reversing the curves, we propose to continue with the present method.

2. *Method of Selecting Patients.* For a time during 1932, Lead IV was taken routinely on all patients over 40 years regardless of diagnosis. Since then it has been taken on all patients on whom a clinical diagnosis of coronary sclerosis, angina pectoris, arteriosclerosis or hypertension had been made or suspected.* In this manner a large mass of electrocardiographic material was assembled.

After having obtained these records, the available clinical histories of the patients were carefully analyzed independently of the electrocardio-

* This was in addition to the patients with suspected recent coronary occlusion (*cf.* Katz and Bohning[8]).

graphic findings. On the basis of the clinical findings alone, a separation of these patients was made into three groups.

Group I, Series A, consisted of 100 patients with clinical findings definitely indicating moderate or advanced coronary sclerosis. The common clinical findings in this group were dyspnea on exertion and precordial pain associated with heart muscle weakness, peripheral arteriosclerosis or a widened aorta. During the preparation of this report a second series of electrocardiograms from 100 patients diagnosed clinically as coronary sclerosis was collected and analyzed. This we have designated Group I, Series B.

Group II consisted of 50 patients in whom coronary sclerosis was at some time suspected, but whose clinical picture was not definite enough to diagnose moderate or advanced coronary sclerosis with certainty or in whom the symptoms could have been caused by another condition.* Groups I and II included both hospital and ambulatory patients.

Group III (added as a control) consisted of 100 patients falling within the required age group, but whose clinical diagnosis was unknown to us. They were ambulatory patients referred for electrocardiograms by physicians from among their private patients. They were all, however, under suspicion of some cardiac involvement and, although the nature of this was undesignated, a fairly varied group of cardiac abnormalities was probably included.

In addition, as a further control we obtained 4-lead electrocardiograms on a group of 25 normal subjects, interns and technicians, and on a group of 133 patients known to have other types of organic heart disease.

In 56 patients of Group I, where a definite diagnosis of coronary sclerosis had been made, repeat 4-lead tracings were obtained at intervals covering from 4 months to more than 2 years.

Results. After separating the records of the patients into the groups outlined above, the electrocardiographic findings of each group were carefully analyzed to determine the frequency of abnormalities. The abnormalities in Lead IV were then studied in detail, classified and correlated with the findings in the other three leads, with the clinical findings and, in the few autopsied cases, with the autopsy findings. For this purpose several extensive correlation tables were assembled from which sundry summary tables were made. In addition the value of the repeated records was estimated.

1. *Frequency of Abnormal and Normal Electrocardiograms in the Several Groups.* The criteria used for the normal Lead IV were those established by the studies of Wolferth and Wood,[4] Katz and Kissin,[5] Masters,[9] Goldbloom[10] and by the analysis of the 25 normal subjects used as controls in this study (Table 1). It can be seen that the various investigators agree rather closely as to the normal limits and our own findings agree fairly well with those of others. From these data the criteria to be used in differentiating a normal from an abnormal Lead IV were determined (Table 2). Variations in the *P* wave were disregarded for the most part as being of little importance. In classifying the standard 3 leads the usual criteria we employ for normality were used (Katz and Johnson[11]).

* Patients with cardiovascular syphilis were excluded from these two groups. In a small series of patients with syphilis, 21 in all, 50% had an abnormal Lead IV.

TABLE 1.—NORMAL VARIATIONS IN AMPLITUDE IN LEAD IV, EXPRESSED IN MILLIMETERS.

Investigator.	No. of cases.	*P* wave.		Primary negative portion of *Q–R–S* or *Q* wave.		Positive portion of *Q–R–S*.		Total amplitude of *Q–R–S*.		*S–T* segment.		*T* wave.	
		Aver.	Range.	Aver.	Range.	Aver.	Range.	Aver.	Range.	Aver.	Range.	Aver.	Range.
Katz and Kissin[5]	25	−0.8	+0.5 to −1.5	−8.5	− 1.0 to −19.0	+12.0	+ 2.0 to +33.0	20.0	5.0 to 34.0	−1.0	0 0 to −2.0	−3.0	+ 1.0 to − 8.0
Masters[9]	104	−0.8	+2.0 to −2.0	−5.3	− 1.5 to −14.0	+10.7	+ 2.5 to +26.0	..	..	−1.0	0.0 to −2.0	−3.3	− 1.0 to − 7.5
Goldbloom[10]	25	−0.6	+1.0 to −2.0	−7.2	− 3.0 to −14.0	+10.8	+ 6.0 to +15.0	..	..	..	..	−4.9	− 2.0 to − 8.0
Bohning and Katz	25	−0.3	+1.0 to −1.0	−7.9	− 2.0 to −15.0	+15.0	+ 6.5 to +24.5	25.1	13.0 to 39.0	−1.3	−0.5 to −2.0	−5.7	− 2.0 to −10.0
Total No. records measured	179	−0.6	+2.0 to −2.0	−7.2	− 1.0 to −19.0	+12.1	+ 2.0 to +33.0	22.5	5.0 to 39.0	−1.1	0.0 to −2.0	−4.2	+ 1.0 to −10.0

NOTE.—In addition Wolferth and Wood,[4] Lieberson and Liberson,[24] Hoffman and Delong[13] have described similar normal types without reporting actual measurements. Their method of applying the electrodes was essentially the same as ours with the anterior electrode near the lower end of the sternum or at the apex and, attached to the right arm terminal. Most cases were taken with the posterior electrode on the back and attached to the left arm terminal. Our cases, however, were all taken on the left leg, which, as we have pointed out in the text, gives essentially the same type of curve.

TABLE 2.—CRITERIA FOR NORMAL LEAD IV AND ABNORMAL VARIATIONS IN LEAD IV.

Record.	*T* wave.	*Q* wave or primary negative portion of *Q-R-S* complex.	Direction of main deflection of *Q–R–S* complex.	*S–T* segment.	*T* wave.
Normal	Negative or diphasic	Always present and usually deep	Diphasic or essentially so (1st deflection neg.)	Occasionally isoelectric, but usually neg. (less than −2 mm.)	Negative (less than −8 mm.).*
Abnormal	1. Isoelectric 2. Positive 3. Polyphasic	1. Very small 2. Absent	1. Entirely pos. (monophasic) 2. Mainly pos. (diphasic) with small neg. 1st deflection 3. Mainly pos. (diphasic) with small neg. end deflection 4. Entirely neg. (monophasic) 5. Mainly neg. (diphasic) with small pos. end deflection 6. Mainly neg. (diphasic) with small pos. 1st deflection 7. Triphasic—W or M types 8. Polyphasic 9. Unusually large 10. Unusually small	1. Neg. (−2 mm. or more) 2. Pos. of any degree	1. Deeply neg. (−8 mm. or more). 2. Barely discernible or flat and isoelectric. 3. Positive. 4. Diphasic, with 1st phase neg. 5. Diphasic, with 1st phase pos. 6. Polyphasic.

* With electrode in the fourth interspace to left of sternum.

The frequency of normal and abnormal electrocardiographic findings in the 3 groups of patients is assembled in Table 3. It can be readily seen that Group I shows a much higher percentage of abnormality in Lead IV and in the conventional 3 leads than is found in either of the other 2 groups. Lead IV showed abnormality most often when the conventional 3 leads were also abnormal. Only 3% of Group I, 8% of Group II and 6% of Group III had normal conventional 3 leads and an abnormal Lead IV. More often a normal Lead IV was present in association with abnormality in the standard 3 leads. This occurred in Group I in 26% of all patients, in Group II in 40% and in Group III in 36%.

TABLE 3.—A COMPARISON OF THE INCIDENCE OF ABNORMALITY IN LEAD IV WITH THAT IN LEADS I, II AND III.

Clinical grouping.	Group I.		Group II.	Group III.
	Series A.	Series B.		
Diagnosis	Coronary sclerosis	Coronary sclerosis	Suspected coronary disease	Undesignated (control group.)
Clinical findings	Definite	Definite	Indefinite	Unknown.
Total number of patients	100	100	50	100
Range of ages, yrs.	40 to 87	36 to 75	30 to 75	35 to 78
Average age, yrs.	59	56	52	54
Lead IV, abnormal	69%	68%	24%	32%
Leads I, II, III, abnormal	92%	83%	56%	62%
Leads, I, II, III, IV, all abnormal	66%	65%	16%	26%
Leads I, II, III, normal; Lead IV, abnormal	3%	3%	8%	6%
Leads I, II, III, abnormal; Lead IV normal	26%	18%	40%	36%

The presence of abnormality in Lead IV in 68.5% of our series of 200 patients with coronary disease is larger than that reported by Goldbloom,[10] who found an abnormal Lead IV in 37.5% of his series of 40 patients with coronary sclerosis. This variation is due largely to the difference in criteria used to establish abnormality of this lead. Goldbloom does not regard a negative T_4 of 9 mm. as abnormal, although from Table 1 it can be seen that only 1 instance of a normal subject out of 179 has yet been reported with a T_4 of 9 mm. or more. Recently, Wood *et al.*[6] found that occasion-

ally T_4 was larger than 9 mm. in their series of normal subjects—but they placed their precordial electrode over the apex. Goldbloom does not interpret a diphasic T_4 as abnormal as we, and most others, do. But most important of all he entirely ignores the S–T_4 deviations, which we and others consider as one of the variations most significant of abnormality. Two mm. was the upper limit of S–T negativity in normal subjects reported in Table 1 and a positive S–T segment was never found in these normal subjects.

The records of a group of 133 instances of patients with organic heart disease of miscellaneous origins were also examined. While similar changes appeared in some of them, the frequency was about one-half that of the 200 cases of coronary sclerosis, and the abnormalities of Lead IV were much less than those found in our series of coronary sclerosis.

While we found that Lead IV alone was diagnostically characteristic in only a few instances when the standard 3 leads were normal, nevertheless Lead IV was of very definite assistance in aiding in the determination of the extent of myocardial damage in many patients. Abnormalities when present in Lead IV are usually striking in appearance and, for this reason, often served as a final clue in evaluating a record which might otherwise be doubtful, if judged by the conventional 3 leads alone. However, just as in the standard leads, different degrees of abnormalities were found varying from the borderline of normality to unquestionable deviations from the normal. Furthermore, greater significance was attached to an abnormality when it occurred associated with other abnormalities, whether in the 4th or the other leads.

2. *Relation of Abnormal Lead IV to the Clinical Findings in the 100 Patients With Coronary Sclerosis (Group I, Series A).* The data of this correlation are assembled in Table 4. The patients were divided into 2 groups, those with normal and those with abnormal Lead IV. It will be seen that dyspnea on exertion and palpitation, cardiac enlargement, edema and congestive heart failure were more frequent in the group with abnormal Lead IV. Furthermore, digitalis therapy was more often required in this group. Pain referable to the heart was present in 85% of all patients, but was only slightly more frequent in the group with abnormal Lead IV. Arteriosclerosis of some type, including peripheral and aortic, was present in 93% of all patients and was about equally distributed between the 2 groups. Hypertension, interestingly enough, was found more frequently in the group with normal Lead IV. The significance of this finding is not clear. In a considerable number of patients a high blood pressure present years earlier had become definitely lower after clinical symptoms of heart muscle weakness had become apparent.

The increased frequency of the finding of dyspnea, palpitation, edema, cardiac failure and cardiac enlargement in patients with

abnormal Lead IV does seem to indicate that these patients had a relatively greater degree of myocardial damage than the group with normal Lead IV. This observation lends support to the view that the appearance of Lead IV is determined by the presence of advanced myocardial involvement and, therefore, can be used as one sign of the presence of this condition.

TABLE 4.—RELATION OF ABNORMALITY IN LEAD IV TO THE CLINICAL FINDINGS IN THE 100 PATIENTS WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

Clinical findings.	Per cent of all cases with		
	Normal Lead IV.	Abnormal Lead IV.	Coronary sclerosis.
Sex:			
Male	61	51	54
Female	39	49	46
Complaints:			
Dyspnea on exertion	48	65	60
Palpitation	22	35	31
Pain, all types	80	87	85
Pain, precordial	77	84	82
Pain, substernal	6	8	8
Pain, radiating to arm	29	19	22
Pain, epigastric	0	3	2
Physical findings:			
Hypertension	76	53	60
Systolic blood pressure:			
Under 100	0	1	1
100 to 150	21	46	39
150 to 180	42	19	26
180 to 200	13	12	12
Over 200	21	22	22
Arteriosclerosis	90	94	93
Cardiac enlargement	48	61	57
Distant heart tones	42	43	43
Systolic murmurs	45	40	42
Diastolic murmurs	3	7	6
Edema	6	21	17
Heart failure of some degree	22	33	30
Cyanosis	9	4	6
Digitalis therapy employed	6	32	24

3. *Relation of Abnormal Lead IV to the Occurrence of Abnormalities in the Standard 3 Leads in the 100 Patients With Coronary Sclerosis (Group I, Series A).* A further estimate of the value of Lead IV can be obtained by comparing the appearance of the standard 3-lead electrocardiogram when this lead is normal and when it is abnormal. This comparison has been summarized in Table 5. The terms used have been those employed by us in interpreting electrocardiograms (Katz and Johnson[11]). It will be seen that the standard 3 leads were not only somewhat more frequently abnormal in the patients with abnormal Lead IV, but the degree of abnormality of the curves was greater, as indicated by the interpretations, "compatible with," "suggests" and "indicates myocardial involvement." The details as to specific aberrations of the several complexes are clearly to be seen in Table 6. Extrasystolic arrhythmias were more frequent in patients with abnormal Lead IV than in

those with this lead normal, and intraventricular and A–V block were not encountered when the 4th lead was normal. There can be no doubt that abnormalities in Lead IV are not only associated more frequently with clinical evidence of myocardial damage, but also with electrocardiographic evidence of such damage in the standard 3 leads. An abnormal Lead IV, this evidence would also suggest, is an additional clue to the electrocardiographic diagnosis of myocardial dosage.

TABLE 5.—RELATION OF ABNORMALITY IN LEAD IV TO THE OCCURRENCE OF ELECTROCARDIOGRAPHIC DEVIATIONS IN THE STANDARD THREE LEADS IN THE 100 PATIENTS WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

Type of deviation.	Per cent of all cases with		
	Normal Lead IV.	Abnormal Lead IV.	Coronary sclerosis.
Leads I, II, III, abnormal	84	96	92
Myocardial involvement:			
Compatible	16	4	8
Suggested	19	12	14
Indicated	49	80	70
Extrasystoles	3	13	10
Auricular fibrillation	3	4	4
Block:			
Intraventricular	0	11	8
Complete A–V	0	1	1
Partial A–V	0	1	1
Q–R–S deviations:			
Slurring	100	100	100
Notching of Q–R–S_1	0	8	6
Notching of Q–R–S_2	3	11	9
Notching of Q–R–S_3	9	39	30
Left axis shift	48	47	47
Left ventricular preponderance	22	30	28
Right ventricular preponderance	0	3	2
Low "voltage" (standard 3 leads)	6	11	10
S–T deviations:			
Negative S–T_1	35	43	41
Negative S–T_2	25	58	34
Negative S–T_3	0	13	9
Positive S–T_1	0	8	6
Positive S–T_2	0	11	8
Positive S–T_3	12	26	22
T deviations:			
Negative T_1	0	20	14
Negative T_2	3	15	11
Negative T_3	32	35	34
Diphasic T_1	13	19	17
Diphasic T_2	3	16	12
Diphasic T_3	10	19	16

4. *The Abnormalities in Lead IV Encountered in the 100 Patients With Coronary Sclerosis (Group I, Series A).* An attempt was made to see if the changes in Lead IV could be divided into several groups. For this purpose the direction and magnitude of the deviation of the various complexes were determined as shown in Table 6. The separation of the group into those with normal and those with

abnormal Lead IV serves to emphasize the criteria used to establish whether the lead was to be classified as normal or abnormal.

TABLE 6.—VARIATIONS IN THE COMPLEXES ENCOUNTERED IN LEAD IV IN THE 100 PATIENTS WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

Complex and type of deviation	Per cent of all cases with		
	Normal Lead IV.	Abnormal Lead IV.	Coronary sclerosis.
P_4:			
Positive	3	8	7
Negative	68	52	60
Isoelectric	29	50	33
Q_4 or primary negative portion of Q–R–S_4:			
Absent	0	10	7
Small (negative)	0	53	36
Medium (negative)	78	14	34
Deep (negative)	22	23	23
Main deflection of Q–R–S_4:			
Monophasic positive	0	7	5
Mainly positive	0	54	37
Diphasic	100	23	47
First deflection positive and small	0	3	2
Mainly negative	0	4	3
Monophasic negative	0	9	6
S–T_4:			
Positive	0	7	5
Isoelectric	29	13	18
Negative	71	80	77
Less than −1 mm.	42	28	32
−1 to −2 mm.	29	31	30
−2 to −4 mm.	0	13	9
−4 to −7.5 mm.	0	8	6
T_4:			
Positive	0	10	7
Diphasic	0	22	15
Negative	100	68	78
−1 to −3 mm.	29	14	19
−3 to −5 mm.	32	16	21
−5 to −8 mm.	29	25	26
−8 to −11 mm.	10	13	12

With this as a background we next classified the records according to the form of the Q–R–S and T complexes encountered in Lead IV. In Table 7 is tabulated the appearance of the other phases of the ventricular complex encountered in each of the Q–R–S and in each of the T types. It is interesting that the second series (B) of 100 cases of coronary sclerosis had a similar distribution.

From this material we next attempted to describe the commoner types of Lead IV seen. This has not been an easy task because of the overlapping and the finer gradations as a survey of Table 7 will show. However, we feel that it is fair to say that 4 main types of abnormality in Lead IV are encountered in coronary sclerosis. We have designated these as (1) the positive Q–R–S_4 type (the most common), (2) the negative Q–R–S_4 type, (3) the positive and diphasic T_4 type and (4) the deeply negative T_4 type. Naturally there is some overlapping between the groups as one of the Q–R–S types

those with this lead normal, and intraventricular and *A–V* block were not encountered when the 4th lead was normal. There can be no doubt that abnormalities in Lead IV are not only associated more frequently with clinical evidence of myocardial damage, but also with electrocardiographic evidence of such damage in the standard 3 leads. An abnormal Lead IV, this evidence would also suggest, is an additional clue to the electrocardiographic diagnosis of myocardial dosage.

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Type of deviation.	Per cent of all cases with		
	Normal Lead IV.	Abnormal Lead IV.	Coronary sclerosis.
Leads I, II, III, abnormal	84	96	92
Myocardial involvement:			
Compatible	16	4	8
Suggested	19	12	14
Indicated	49	80	70
Extrasystoles	3	13	10
Auricular fibrillation	3	4	4
Block:			
Intraventricular	0	11	8
Complete *A–V*	0	1	1
Partial *A–V*	0	1	1
Q–R–S deviations:			
Slurring	100	100	100
Notching of $Q–R–S_1$	0	8	6
Notching of $Q–R–S_2$	3	11	9
Notching of $Q–R–S_3$	9	39	30
Left axis shift	48	47	47
Left ventricular preponderance	22	30	28
Right ventricular preponderance	0	3	2
Low "voltage" (standard 3 leads)	6	11	10
S–T deviations:			
Negative $S–T_1$	35	43	41
Negative $S–T_2$	25	58	34
Negative $S–T_3$	0	13	9
Positive $S–T_1$	0	8	6
Positive $S–T_2$	0	11	8
Positive $S–T_3$	12	26	22
T deviations:			
Negative T_1	0	20	14
Negative T_2	3	15	11
Negative T_3	32	35	34
Diphasic T_1	13	19	17
Diphasic T_2	3	16	12
Diphasic T_3	10	19	16

4. *The Abnormalities in Lead IV Encountered in the 100 Patients With Coronary Sclerosis (Group I, Series A).* An attempt was made to see if the changes in Lead IV could be divided into several groups. For this purpose the direction and magnitude of the deviation of the various complexes were determined as shown in Table 6. The separation of the group into those with normal and those with

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	Normal Lead IV.	Abnormal Lead IV.	Coronary sclerosis.
P_4:			
Positive	3	8	7
Negative	68	52	60
Isoelectric	29	50	33
Q_4 or primary negative portion of Q–R–S_4:			
Absent	0	10	7
Small (negative)	0	53	36
Medium (negative)	78	14	34
Deep (negative)	22	23	23
Main deflection of Q–R–S_4:			
Monophasic positive	0	7	5
Mainly positive	0	54	37
Diphasic	100	23	47
First deflection positive and small	0	3	2
Mainly negative	0	4	3
Monophasic negative	0	9	6
S–T_4:			
Positive	0	7	5
Isoelectric	29	13	18
Negative	71	80	77
Less than −1 mm.	42	28	32
−1 to −2 mm.	29	31	30
−2 to −4 mm.	0	13	9
−4 to −7.5 mm.	0	8	6
T_4:			
Positive	0	10	7
Diphasic	0	22	15
Negative	100	68	78
−1 to −3 mm.	29	14	19
−3 to −5 mm.	32	16	21
−5 to −8 mm.	29	25	26
−8 to −11 mm.	10	13	12

With this as a background we next classified the records according to the form of the Q–R–S and T complexes encountered in Lead IV. In Table 7 is tabulated the appearance of the other phases of the ventricular complex encountered in each of the Q–R–S and in each of the T types. It is interesting that the second series (B) of 100 cases of coronary sclerosis had a similar distribution.

From this material we next attempted to describe the commoner types of Lead IV seen. This has not been an easy task because of the overlapping and the finer gradations as a survey of Table 7 will show. However, we feel that it is fair to say that 4 main types of abnormality in Lead IV are encountered in coronary sclerosis. We have designated these as (1) the positive Q–R–S_4 type (the most common), (2) the negative Q–R–S_4 type, (3) the positive and diphasic T_4 type and (4) the deeply negative T_4 type. Naturally there is some overlapping between the groups as one of the Q–R–S types

TABLE 7.—TABULATION OF ABNORMALITIES FOUND IN LEAD IV IN 100 PATIENTS WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

				Associated findings in the ventricular complex in Lead IV.											
				Q wave.*		*S–T* deviation.				*T* wave.					
								Negative.			Diphasic.		Negative.		
			No.	Absent.	Present.	Positive.	Isoelectric	−2 mm. or less.	More than −2 mm.	Positive	1st phase positive.	1st phase negative.	Less than −8 mm.	−8 mm. or more.	Intraventricular block (*Q–R–S* prolonged).
I on the basis of the form of *Q–R–S*$_4$	*Q–R–S*$_4$ positive	Entirely pos.	5	5	0	0	0	2	3	1	0	1	0	3	2
		Mainly pos.	37	0	37	0	2	25	10	0	0	1	30	6	1
		Total	42	5	37	0	2	27	13	1	0	2	30	9	3
	Q–R–S$_4$ diphasic	1st deflection neg.†	16	0	16	1	4	10	1	3	2	8	2	1	1
	Q–R–S$_4$ negative	Entirely neg.	6	0	6	3	2	1	0	2	2	0	2	0	3
		Mainly neg., 1st phase neg.	3	0	3	1	1	1	0	0	0	1	2	0	0
		Mainly neg., 1st phase pos.	2	2‡	0	0	0	2	0	0	1	0	1	0	2
		Total	11	2	9	4	3	4	0	2	3	1	5	0	5
II on the basis of the form of *T*$_4$	*T*$_4$ positive	*Q–R–S*$_4$ mainly pos.	1	1	0	0	0	1	0	1	..	..	..	..	0
		Q–R–S$_4$ diphasic, 1st ph. neg.	3	0	3	0	3	0	0	3	..	..	..	..	0
		Q–R–S$_4$ mainly neg.	2	0	2	1	1	0	0	2	..	..	..	..	2
		Total	6	1	5	1	4	1	0	6	..	..	..	..	2
	T$_4$ diphasic 1st phase negative	*Q–R–S*$_4$ mainly pos.	2	1	1	0	0	2	0	..	0	2	..	..	0
		Q–R–S$_4$ diphasic, 1st ph. neg.	8	0	8	0	0	7	1	..	0	8	..	..	1
		Q–R–S$_4$ mainly neg.	1	0	1	1	0	0	0	..	0	1	..	..	0
		Total	11	1	10	1	0	9	1	..	0	11	..	..	1
	T$_4$ diphasic 1st phase positive	*Q–R–S*$_4$ mainly pos.	0	0	0	0	0	0	0	..	0	0	..	..	0
		Q–R–S$_4$ diphasic, 1st ph. neg.	2	0	2	1	1	0	0	..	2	0	..	..	0
		Q–R–S$_4$ mainly neg.	3	1‡	2	2	0	1	0	..	3	0	..	..	2
		Total	5	1	4	3	1	1	0	..	5	0	..	..	2
	T$_4$ diphasic both types	Total	16	2	14	4	1	10	1	..	5	11	..	..	3
	T$_4$ negative	*Q–R–S*$_4$ mainly pos.	39	3	36	0	2	24	13	..	..	..	30	9	3
		Q–R–S$_4$ diphasic, 1st ph. neg.	3	0	3	0	0	3	0	..	..	..	2	1	0
		Q–R–S$_4$ mainly neg.	5	1‡	4	0	2	3	0	..	..	..	5	0	1
		Total	47	4	43	0	4	30	13	..	..	..	37	10	4
		Grand total	69	7	62	5	9	41	14	6	5	11	37	10	9

* First negative portion of *Q–R–S*$_4$.
† No instance was found with 1st phase positive.
‡ First deflection of *Q–R–S*$_4$ complex is positive.

may be associated with one of the *T* types. The criteria by which each type is classified and the appearance of the other phases of the ventricular complex encountered are summarized in Table 8 and are illustrated in Figs. 1 to 17.

TABLE 8.—SUMMARY OF THE MOST COMMON ABNORMAL TYPES OF LEAD IV FOUND IN 200 PATIENTS WITH CORONARY SCLEROSIS.

	No. found	Associated findings in other phases of ventricular complex.				Remarks.	Illustrated in Fig.
		Q wave or primary negative portion of *Q–R–S*$_4$.	Main direction of *Q–R–S*$_4$ complex.	*S–T*$_4$ segment.	*T*$_4$ wave.		
(1) *Q–R–S*$_4$ positive type	83	Absent or small	Entirely or mainly pos.	Usually neg. and ranges from −1 to −8 mm.	Usually neg.; mod. to deep (occ. diphasic and rarely pos.)	Most common type (assoc. with E.C.G. evidence of myocardial involvement in standard leads)	3 4 5 7 8 9 10 12
(2) *Q–R–S*$_4$ negative type	16	Usually present and deep	Entirely or mainly neg. (sometimes a small pos. deflection precedes main neg. deflection)	Varies—may be pos., isoelectric or neg.	Varies—most often neg., more rarely pos. or diphasic with 1st phase neg.	Not so common (often associated with intraventricular block)	6 14 15 *A, B* 16 *A, B*
(3) *T*$_4$ positive or diphasic type	50	Usually present and small, may be absent	Varies — frequently diphasic, but may be pos. or neg.	Varies — usually neg. but may be isoelectric or pos.	Pos. or diphasic (usually of type having 1st phase neg.)	Resembling the type with ant. wall infarction, as seen in recent coronary occlusion	5 7 8 9 10 *A* 13 *C* 15 *B* 16 *A, B*
(4) *T*$_4$ deeply negative type	14	Usually present; may be mod. deep or absent	Usually mainly pos.; often diphasic	Neg.; often deeply neg.	Deeply neg. (−8 to −15 mm.)	Resembling the type with post. wall infarction, as seen in recent coronary occlusion	11

In the *positive Q–R–S*$_4$ *type*, which occurred 83 times in the 200 cases, the *Q–R–S* complex was mainly or entirely positive (Figs. 3, 4, 5, 7, 8, 9, 10, 12). The former was the more usual form, the *Q* wave or primary negative portion of *Q–R–S* being present, but small. In 7 instances the *Q–R–S* complex was entirely positive (Figs. 8, 9). At times a W form was seen (Fig. 5). The *S–T* segment was usually within normal limits (Figs. 3, 5, 10, 12) but in 20 records was definitely negative (Figs. 4, 7, 8, 9). The *T* wave was usually within normal limits (Figs. 3, 4, 10 *B*, 12 *A, B, C*), but once was positive (Fig. 5), 15 times diphasic (Figs. 7, 8, 9, 10 *A*) and 11 times deeply negative. This positive *Q–R–S*$_4$ type was found in patients with intraventricular block only 6 times.

In the *negative Q–R–S*$_4$ *type*, which occurred 16 times in 200 cases, the *Q–R–S* complex was mainly or entirely negative (Figs. 6, 14, 15, 16). In 6 instances the *Q–R–S* complex was entirely negative

(Figs. 14 *B*, 15 *B*). In 8 the complex was diphasic, with the 1st phase negative (a deep *Q*) (Figs. 14 *A*, 15 *A*). In the other 2 the 1st phase was small and positive (Fig. 16 *A*, *B*). At times an M form was seen (Figs. 6, 14 *B*) or a W form (Fig. 15 *B*, *C*). The

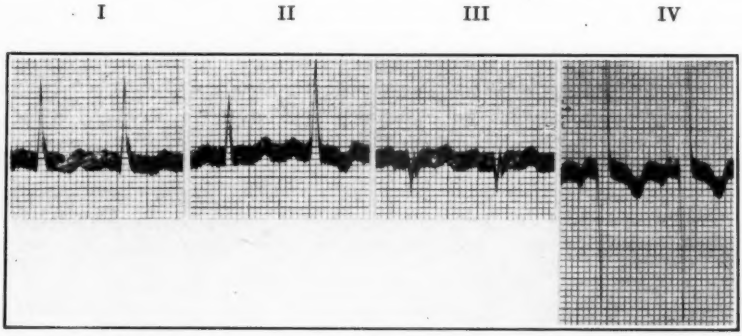

FIG. 1.—Moderate coronary sclerosis, moderate myocardial fibrosis and fatty infiltration of the myocardium found at autopsy. Note the large amplitude of Q–R–S_4 which is the only abnormality in this lead. There is slurring in the standard 3 leads, a negative S–T_1 and a positive S–T_3, left axis shift and a late ventricular extrasystole in Lead II. In this and subsequent figures the 4 leads are indicated by Roman numerals.

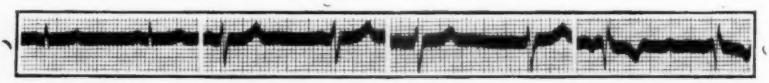

FIG. 2.—Moderate coronary sclerosis, moderate myocardial fibrosis, fatty infiltration of the right ventricle and brown atrophy of the heart found at autopsy. Note the small amplitude of Q–R–S_4 which is the only abnormality in this lead. There is a decided left axis shift in the standard 3 leads.

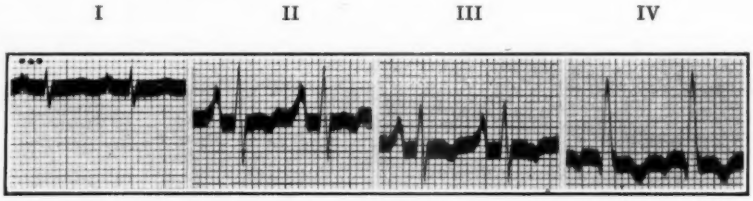

FIG. 3.—Moderate coronary sclerosis and moderate myocardial fibrosis found at autopsy. Note the positive Q–R–S_4 type which is the only abnormality in this lead. There is a peculiar diphasic Q–R–S in the standard leads, negative T_2 and T_3 and large P_2 and P_3.

S–T segment was usually within normal limits (Figs. 6, 14, 15 *C*, *D*, 16), but in 4 instances it was positive (Fig. 15 *B*). The T wave was within normal limits in 10 instances (Figs. 6, 14 *A*, 15 *E*) and positive or diphasic in the remaining 6 (Figs. 15, 16). There were 5 instances of intraventricular block in this group (Figs. 15, 16).

Neither one of the two Q–R–S_4 types was constantly associated with either one of the Q types described in the standard 3 leads by Wilson *et al.*[2]

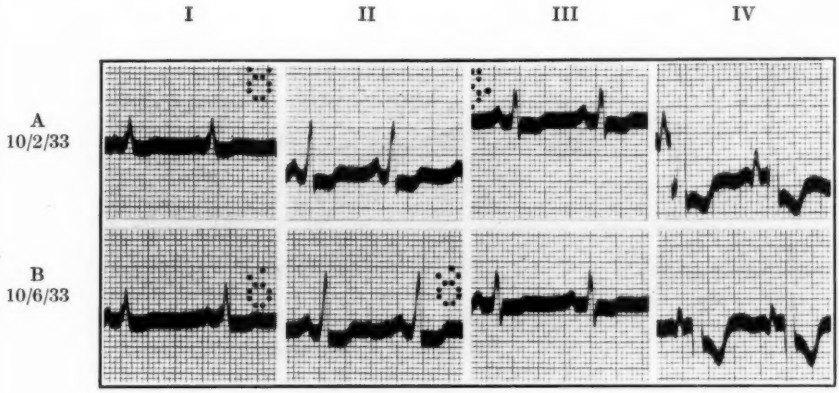

FIG. 4.—Moderate coronary sclerosis and moderate myocardial fibrosis found at autopsy. The 2 records were taken just before the patient's death. Note the positive Q–R–S_4 type, the markedly depressed S–T_4 and the positive P_4, which are all abnormal. The Q–R–S is slurred in the standard 3 leads, S–$T_{1, 2}$ and $_3$ is depressed and $T_{1, 2}$ and $_3$ is not discernible.

In the *positive and diphasic T_4 type*, which occurred 50 times in 200 cases, the T wave was positive in 13 (Figs. 5, 9 E) diphasic with the 1st phase negative in 30 instances (Figs. 7, 8, 9, 10 A) and diphasic with the 1st phase positive in 7 (Figs. 13 C, 15 B, 16 B). The Q–R–S complex was usually diphasic and not abnormal (Fig. 13 C), although there were 16 instances with a positive Q–R–S_4

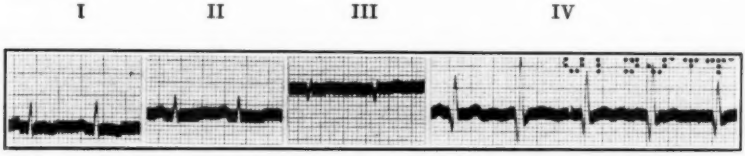

FIG. 5.—Moderate coronary sclerosis and moderate myocardial fibrosis found at autopsy. Note the positive Q–R–S_4 and positive T_4 types with W-shaped Q–R–S complex and electrical alternans. There is low "voltage" in the standard 3 leads, left axis shift, slightly depressed S–T_1 and $_2$ and negative T_1.

type (Figs. 5, 7, 8, 9, 10 A) and 4 with a negative Q–R–S_4 type (Figs. 15 B, 16). The S–T segment was usually within normal limits (Figs. 10 A, 16). It was deeply negative 8 times (Figs. 7, 8 9) and positive 8 times (Figs. 13 C, 15 B). There were 6 instances of intraventricular block in this group (Figs. 13 C, 15, 16). This group was associated with a negative T_1 or the T_1 type of Parkinson and Bedford[12] only 5 times.

In the *deeply negative T_4 type*, which occurred 14 times in 200 cases, the T wave was 8 mm. or more in depth (Fig. 11). In all but 3 instances this was associated with the positive Q–R–S_4 type (Fig. 11). In the exceptions the Q–R–S complex was diphasic and normal. The S–T segment was always negative, but in only 8 instances was it outside normal limits. There were 4 instances of intraventricular block, all with a positive Q–R–S_4 type. This group was occasionally (5 instances) associated with a negative T_3 or the T_3 type, (Parkinson and Bedford[12]).

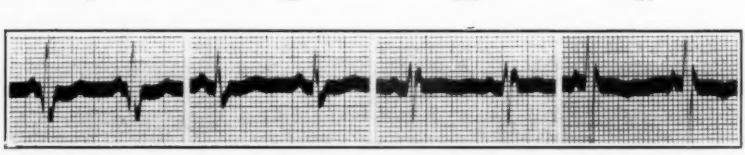

FIG. 6.—Moderate coronary sclerosis, myocardial fibrosis and syphilitic aortitis found at autopsy. Note the negative Q–R–S_4 type with M-shaped Q–R–S complex. There is intraventricular block of the indeterminate type, with Q–R–$S_{1, 2}$ and $_3$ slurred and Q–R–S_3 inverted. S–T_1 is depressed and S–T_3 elevated.

Several other abnormalities were observed. The diphasic Q–R–S_4 was sometimes unusually large (Fig. 1) or unusually small (Fig. 2) or was the mirror image of normal in that the 1st phase was positive and was followed by a negative phase of equal magnitude (Fig. 16 *C*).

5. *The Appearance of Lead IV in the Presence of Certain Abnormalities of the Standard 3 Leads in the 100 Patients With Coronary Sclerosis* (*Group I, Series A*). Of the 100 patients with coronary

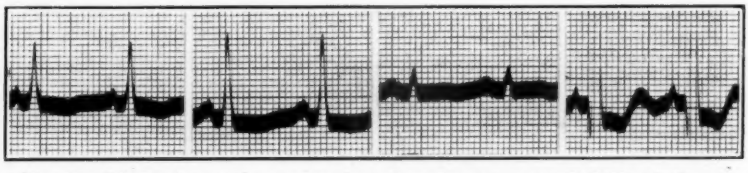

FIG. 7.—Moderate coronary sclerosis and moderate myocardial fibrosis found at autopsy. Note the positive Q–R–S_4 and diphasic T_4 types, the markedly depressed S–T_4 and positive P_4. There is slurring of Q–R–$S_{1, 2}$ and $_3$, depression of S–T_1 and $_2$, small $T_{1, 2}$ and $_3$ and inversion of T_1 and $_2$.

sclerosis in Series A, 75 showed a left axis shift or a left ventricular preponderance, but this did not noticeably influence the direction of the major Q–R–S deflection in Lead IV. It is interesting that 33 of the 39 instances of the positive Q–R–S_4 type without intraventricular block were in this group and only 1 of the 6 instances of the negative Q–R–S_4 type without intraventricular block was in this group. This agrees with the observations of Masters,[9] who

found that left axis shift had little influence on the direction of Q–R–S_4 complex.

Low "voltage" of Q–R–S in the standard 3 leads which occurred 10 times in this series was never associated with low amplitude in Lead IV.

There were 14 instances of the T_1 type of Parkinson and Bedford and 35 instances of the T_3 type in this series. These were associated with the various types of Lead IV as well as with a normal Lead IV.

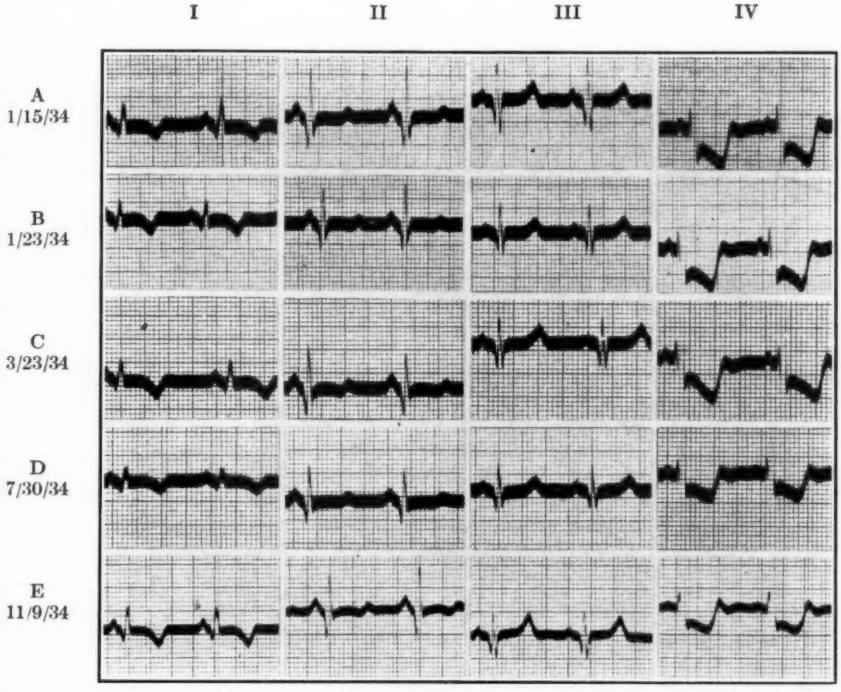

FIG. 8.—Chronic non-progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the practically constant appearance of the 4 leads over a period of 10 months. Note also the positive Q–R–S_4 and diphasic T_4 types, the markedly depressed S–T_4 and the positive P_4. Q–R–$S_{1, 2}$ and $_3$ is slurred. There is a Q_1 and in later records a Q_2, S–T_3 is elevated slightly.

The same was true of the 27 instances of the Q_1 of Wilson and the 35 instances of the Q_3 type in this series.

Masters[9] has suggested that Lead IV might be of service in differtiating T_3 inversions, which are a normal variant from those which are indicative of abnormality. In Series A of our cases of coronary sclerosis, there were 34 instances of negative T_3, 24 of which had an abnormal Lead IV.

There were 9 patients with intraventricular block of the common

bundle-branch type or indeterminate type in Series A. Five of these had a negative Q–R–S_4 type, some being of the common bundle-branch type, others of the indeterminate. In the latter, the Q–R–S_4 resembled a W and was small (Fig. 15 *B*). Three of the others which were of the common type of bundle-branch block showed the positive Q–R–S_4 type. The 9th, of the indeterminate type, had a diphasic Q–R–S_4 complex. Hoffman and Delong[13] reported that in their 6 cases of bundle-branch block the Q–R–S_4

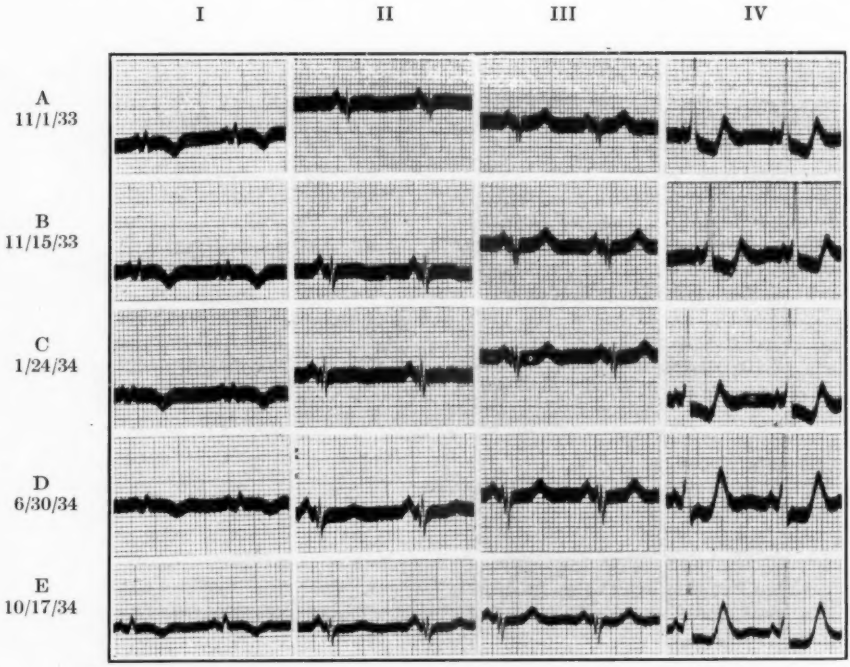

FIG. 9.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the slow progression of the T wave in Lead IV over a period of a year. Note the positive Q–R–S_4 and diphasic and positive T_4 types, the markedly depressed S–T_4 and eventually positive P_4. Q–R–$S_{1, 2}$ and $_3$ are small, slurred and there is a left axis shift; T_1 is inverted.

was normal except for widening of the Q–R–S. It is difficult to say what significance the various types of Q–R–S_4 encountered in intraventricular block may have; but in view of the recent studies by Wilson *et al.* with precordial leads[14] and the observation made on the Q–E interval by Nichol,[15] Wolferth *et al.*[16] and Katz, Landt and Bohning,[17] it is possible that the 4th lead may be found to be of value in helping to determine the location of the intraventricular block. This we are now investigating further.

6. *The 4-lead Electrocardiogram in Patients With Coronary Sclerosis Confirmed at Postmortem.* There is very little information in the literature concerning the 4-lead electrocardiogram in instances of coronary sclerosis confirmed at autopsy. We are, therefore, reporting our findings in 7 such instances, the clinical diagnosis of coronary sclerosis having been confirmed postmortem by Dr. O. Saphir, of the Department of Pathology. The sclerosis was found

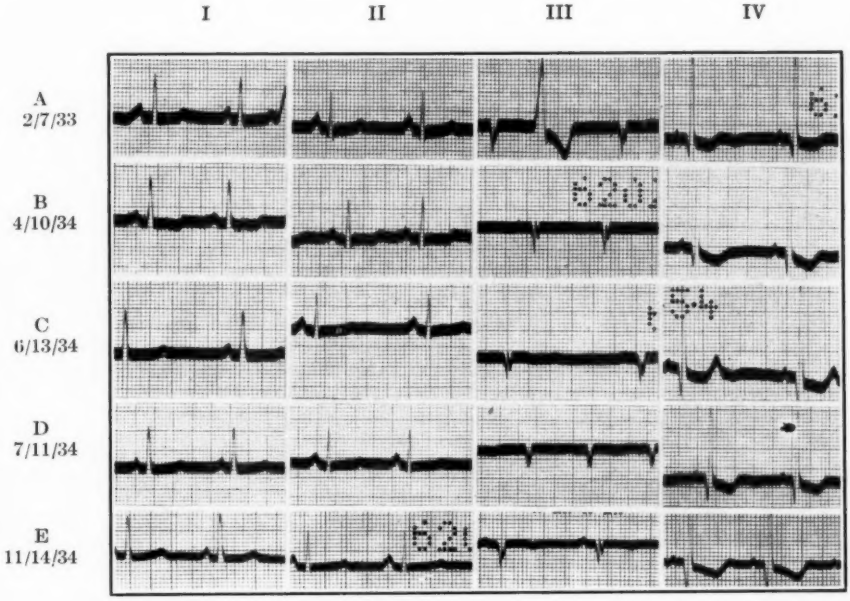

FIG. 10.—Chronic non-progressive coronary insufficiency on which is superimposed a subacute coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis who had an attack of clinically diagnosed recent coronary occlusion in June, 1934. Note the practically constant appearance of Lead IV over a period of 1 year and 5 months except for the temporary change in segment C when the patient had coronary occlusion. The change consisted in the appearance of a positive T_4 type with some depression of S–T_4, the standard 3 leads showing no change. The record shows a positive Q–R–S_4 type and in Segment A, a diphasic T_4 type. There is a noticeable sinus arrhythmia. In Lead III of Segment A there is a ventricular extrasystole. There is left axis shift. S–T_1 and $_2$ is depressed and $T_{1,\ 2}$ and $_3$ is small.

to be moderate to advanced in all 7 and was associated with moderate or extensive myocardial fibrosis. The important detailed findings are given in the legends of Figs. 1 to 7.

In none of the 7 was Lead IV normal. In one the abnormality consisted of a tremendously large diphasic Q–R–S_4 (43 mm.) associated with a negative S–T_1, slurred Q–R–$S_{1,2,3}$ and left axis shift (Fig. 1). In a 2d the abnormality consisted of a small Q–R–S_4

associated with a left ventricular preponderance (Fig. 2).* In a 3d instance the abnormality consisted of a positive Q–R–S_4 type accompanied by several abnormalities in the standard 3 leads, especially large P_2 and $_3$ (Fig. 3). In a 4th the abnormality in Lead IV consisted of a marked depression of the S–T segment associated with similar S–T depressions in the other 3 leads; a positive Q–R–S_4 type and a positive P_4 were also present (Fig. 4). The changes between records in this case are probably due to the moribund condition of the patient. In a 5th the Q–R–S_4 was mainly up and triphasic (W), and was associated with the positive T_4 type (Fig. 5). Low "voltage," a left axis shift, S–T depressions in Leads I and II were also present. Another interesting feature is found in an electrical alternans in Lead IV. In the 6th the abnor-

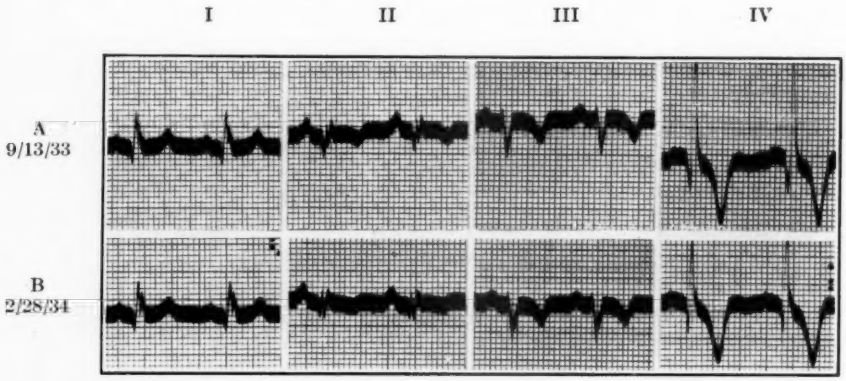

FIG. 11.—Chronic non-progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the practically constant appearance of the 4-lead electrocardiogram over a period of 5½ months. Note the positive Q–R–S_4 and the deeply negative T_4 types. The Q–R–S complex is notched and small in Leads I, II and III, a Q_1 is present and there is left axis shift; T_1 and $_2$ is inverted.

mality consisted of an indeterminate intraventricular block with a negative Q–R–S_4 type, the complex being triphasic and M shaped (Fig. 6). In the 7th, the abnormality consisted of a markedly depressed S–T_4, a diphasic T_4 (1st phase negative) and Q–R–S_4 mainly up (Fig. 7). The standard 3 leads were also abnormal.

This small series of autopsied cases, we believe, confirms the interpretation that Lead IV is of value in helping determining the status of the coronary circulation.

7. *The Value of Serial 4-lead Electrocardiograms in Coronary Disease.* Early during the course of this study we were impressed with the resemblance of some of Lead IV's obtained in patients with

* This was a very interesting finding since brown atrophy was present. This has been dealt with elsewhere by Katz, Saphir and Strauss.[18]

coronary sclerosis to those seen following a coronary occlusion, but unlike the latter, these aberrations persisted practically unchanged for months or changed slowly. This was especially true of the group of records showing the positive or diphasic T_4 type (Figs. 8, 9). Patients with a recent coronary occlusion and myocardial infarction show abnormalities which progress and then regress rather rapidly in one or more of the leads of the 4-lead electrocardiograms and usually in Lead IV. For example, a negative T_4 following the occlusion, becomes diphasic, then positive and later, over a

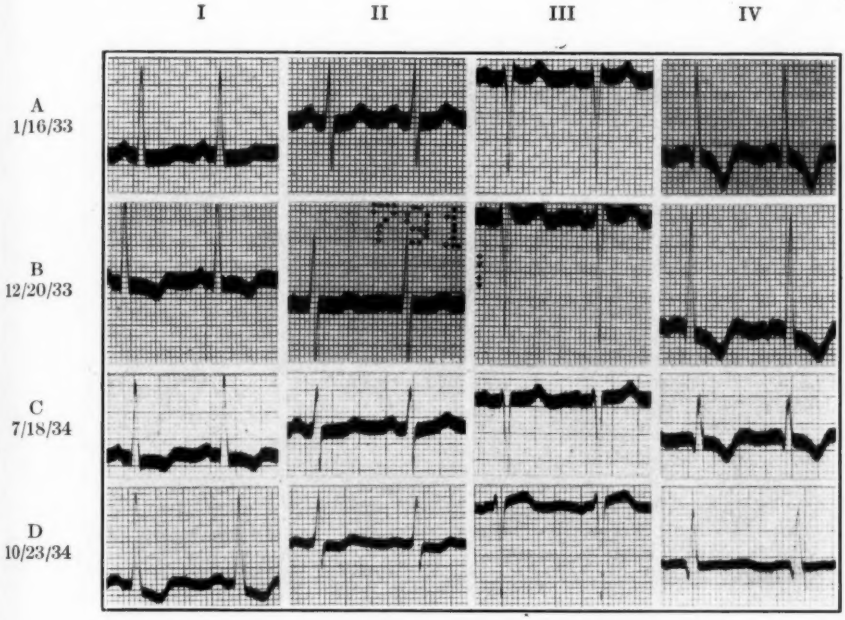

FIG. 12.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the slowly progressive decrease in Q–R–S_4 and the decrease in size of T_4 associated with progressive depression of S–T_1 and $_2$ and elevation of S–T_3 over a period of 1 year and 9 months. Note the positive Q–R–S_4 type associated with left ventricular preponderance, depressed S–T_1 and $_2$, elevated S–T_3 and negative T_1.

period of weeks, reverts back to a normal negative T wave (Katz and Bohning[8]). For example, in Fig. 10 is shown a patient with coronary sclerosis with a diphasic or negative T_4 (Segments A and B) which became peaked and positive (Segment C) following an occlusion with myocardial infarction, and then in a few weeks reverted to its earlier form (Segment D). In striking contrast, the patients with coronary sclerosis maintained the diphasic or positive T wave in Lead IV for many months or over 1 year or more either unchanged or only slowly progressive (Figs. 8, 9).

These observations led us to study the changes in serial electrocardiograms systematically. A collection of serial electrocardiograms covering a period from 4 months to 2 years or more were obtained in 56 of the 200 patients with coronary sclerosis. An analysis of these records and, in addition, those obtained on patients with recent coronary occlusion and records obtained during this period in other conditions have led us to the following conclusion:

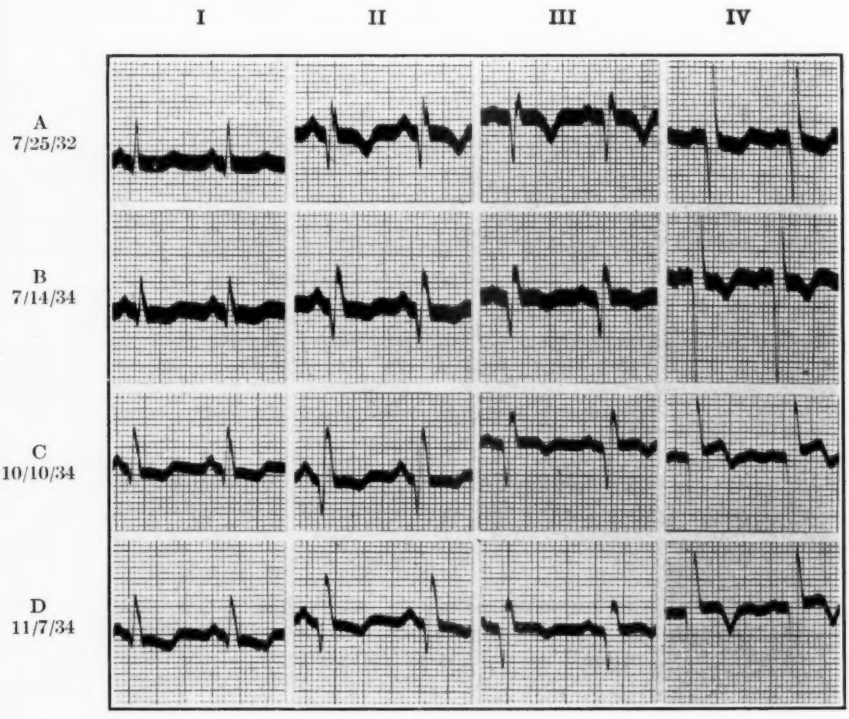

FIG. 13.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the progressive increase in Q–R–S duration, the S–T_4 elevation, the change from a diphasic T_4 with 1st phase negative to a diphasic T_4 with 1st phase positive over a period of 2 years and 3 months. This is associated with an inversion of T_1, decreased inversion of T in Leads II and III and depression of S–$T_{2 \text{ and } 2}$, elevation of S–T_3. There is an indeterminate type of intraventricular block and Q_2 and Q_3 is present.

If one excludes records obtained from acute infectious cases, from moribund patients, and if one can exclude the effect of large doses of digitalis (Strauss and Katz[19]), then from the changes in serial 4-lead electrocardiograms it can be determined whether the coronary insufficiency is: (1) An acute coronary insufficiency, *i. e.*, angina pectoris, nocturnal dyspnea, cardiac asthma, or its equivalent; (2) a subacute coronary insufficiency, *i. e.*, recent occlusion, thrombotic or

arteriosclerotic with myocardial infarction; (3) a chronic non-progressive coronary insufficiency; or (4) a chronic progressive coronary insufficiency.

In acute coronary insufficiency which is usually superimposed on a chronic milder coronary insufficiency the changes in the 4-lead electrocardiogram are transitory and usually slight, such as occur following exercise in patients with chronic coronary insufficiency (Katz and Landt[20]) These changes are transitory, lasting only for a few minutes or hours after which the 4-lead electrocardiogram returns to its preëxisting contour. We have seen 7 instances where this has occurred spontaneously. In some, these changes were accompanied by attacks of angina pectoris. In others, no angina pectoris accompanied the condition but, instead, only vague symp-

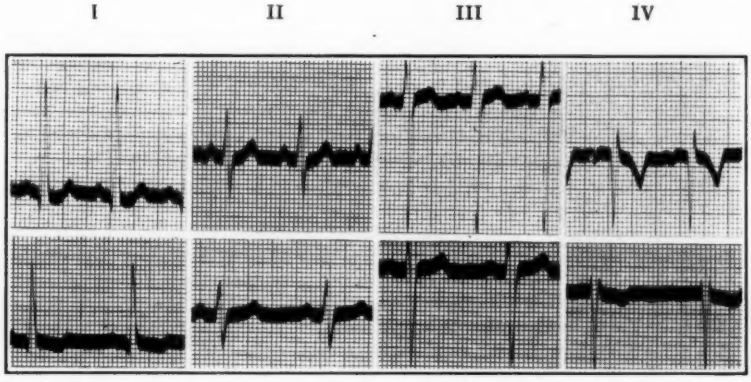

FIG. 14.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the decrease in T over a period of 1 year and 8 months, associated with inversion of T_1. Note the negative Q–R–S_4 type which in Segment B is M shaped. There is left ventricular preponderance and depressed S–T_1 and elevated S–T_3.

toms occurred. It is possible that similar changes will occur when the patient has an attack of paroxysmal cardiac dyspnea. We believe that such changes in the electrocardiogram are brought about by any condition in which the coronary blood supply becomes inadequate for the work the heart is doing, either because the former declines suddenly or the latter increases abruptly. Factors which bring about such a disbalance have been discussed elsewhere (Katz[21]).

In the subacute coronary insufficiency, the inadequacy of the coronary circulation persists long enough to cause myocardial infarction. This may be due to thrombotic closure, to arteriosclerotic closure, or to arteriosclerotic narrowing and congestive heart failure (Saphir, Priest, Hamburger and Katz[3]). Here the changes in the electrocardiogram are more marked and progress over a period of days, weeks or a month or more if the patient survives,

before returning toward normal. This is the period of time required to establish an adequate collateral circulation. This group is discussed in detail elsewhere (Katz and Bohning[8]).

In the chronic non-progressive coronary insufficiency, the 4-lead electrocardiogram shows abnormalities which are practically stationary over long periods of time, months or years. We have 36 instances of this group (Figs. 8, 10 *A*, *D*, 11). In this group it would seem that the collateral circulation keeps pace with the inadequacies

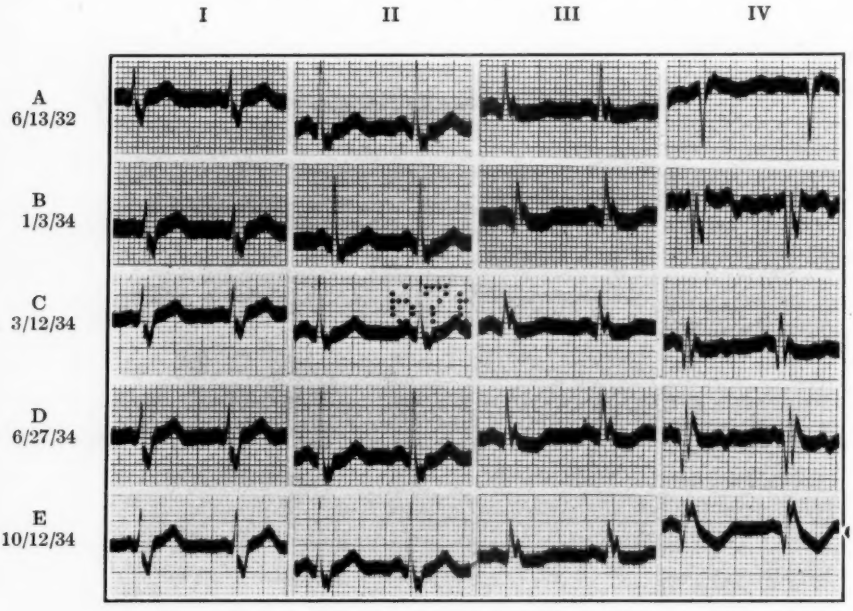

FIG. 15.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the progressive change in contour of Lead IV over a period of 2 years and 4 months. Note that the negative Q–R–S_4 type changes to a diphasic type, that in Segment B the Q–R–S_4 has a W form, that the positive S–T_4 becomes negative, that the diphasic T_4 becomes negative, that P_4 becomes positive and that the S–T becomes positive in Lead I and negative in Lead III. There is an intraventircular block of the indeterminate type.

of the circulation either because, on the one hand, the pathologic changes are developing slowly or not at all, or, on the other hand, because the impairment is not too far advanced so that the collateral circulation can keep pace with the pathologic process. In any event the outlook in such patients, other things being equal, should be better barring the intervention of a thrombus, than in the succeeding group.

In the chronic progressive coronary insufficiency, the 4-lead electrocardiograms show abnormalities which progress slowly over

a period of months, or a year or more. We have 20 instances of this group in this series (Figs. 9, 12, 13, 14, 15, 16 and 17). In this group the collateral circulation cannot keep pace with the pathological process either because the anatomic changes are far advanced or because cardiac congestive failure is occurring.

It must be borne in mind that, while the last group includes for the most part the more abnormal electrocardiograms, nevertheless, there is no correlation between the degree of electrocardiographic abnormality and the rate of progression of the abnormalities (*cf.* Figs. 8, 17). Serial electrocardiograms, we believe, should be taken in all

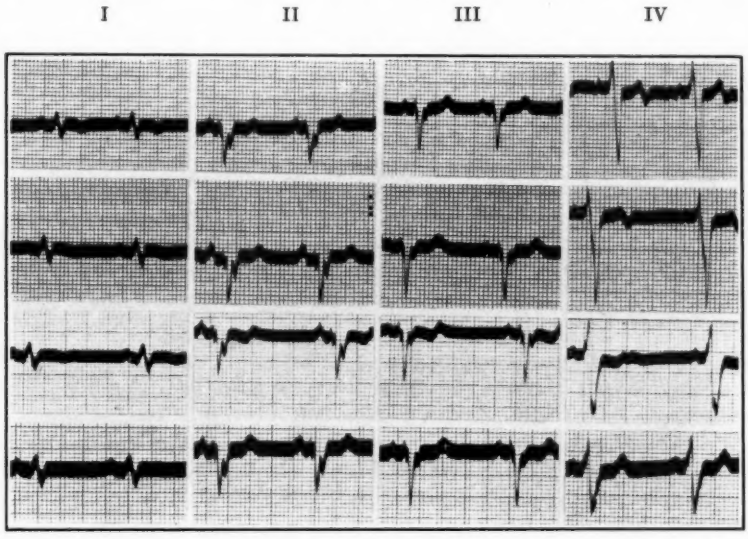

FIG. 16.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note that the S–T segment in Lead IV becomes depressed and the diphasic T_4 becomes positive over a period of 13 months, at the same time that T_2 and $_3$ become diphasic and P_4 positive. There is an intraventricular block of the common bundle-branch type. Note that in Segments A and B there is a negative Q–R–S_4 type and in Segment C, a diphasic Q–R–S; in all, however, the 1st phase is positive.

patients suspected of chronic coronary insufficiency and an estimate made of the degree of the inadequacy of the circulation and the rate of progression from the records so obtained. This estimate, we believe, is of decided assistance to the clinician when correlated with his judgment based on his clinical findings. We believe that this electrocardiographic evaluation is particularly useful because of the paucity of the clinical evidence in a large group of such patients. Indeed, further studies along these lines may offer a useful aid in prognostic studies as, for example, life insurance evaluations. We have pointed out elsewhere the added value of a graded exercise test for this purpose (Katz and Landt[20]).

Finally, it may be emphasized that the 4th lead is a definite aid, not because the abnormalities are confined to this lead alone, but because the changes are so often more noticeable in this lead than in the others. Furthermore, the deviation from normal in this lead often bears a reciprocal relationship to the deviation from normal in the standard 3 leads.

The changes in the 4-lead electrocardiogram seen in coronary disease are expressions of damages to the myocardium brought on by inadequacies of the coronary circulation. The S–T deviations are due to injury currents set up in various parts of the muscle mass as a result of injury to the myocardium. These currents actually disappear once the injured tissue is dead (Korey and Katz[22]). The T-wave changes are brought about by a long delay in the arrival of the impulse to the injured areas (Katz[23]). Conduction is the

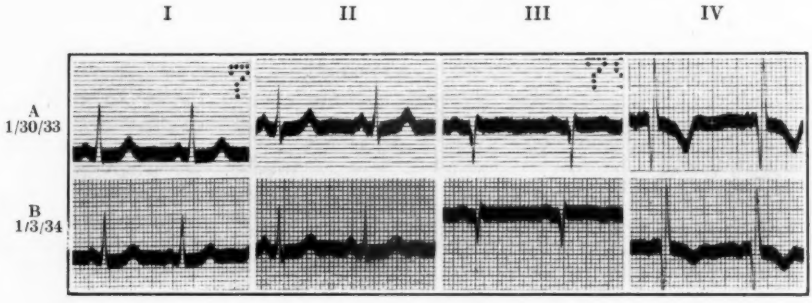

FIG. 17.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note that while both records of Lead IV are normal there is a change between them, *viz.*, T_4 is smaller in Segment B and S–T_4 formerly depressed is now isoelectric. This change occurred over a period of 11 months and is associated with S–T_1 and $_2$ depression and decrease in T_1 and $_2$. There is left axis shift in Q_3 and slurring of Q–R–S_1, $_2$ and $_3$.

most labile physiologic property of the heart and the first to be affected and the last to return to normal when cardiac muscle is damaged or malnourished.* These facts offer a rational explanation of the correlation we have established between the electrocardiographic changes and the degree and course of the coronary insufficiency. This functional classification should prove as useful in evaluating the clinical course of the patients as the anatomic and etiologic classifications.

Summary. 1. A total of 508 electrocardiograms taken with a Lead IV have been analyzed and the data tabulated and summarized. Two hundred were from patients clinically diagnosed to have coronary sclerosis, 50 from patients suspected of having coronary sclerosis but without definite symptoms, 100 from patients with

* The Q–R–S abnormalities have been explained by Wilson *et al.*[2] as the result of the absence of the electrical effects of the destroyed areas.

suspected cardiac disease, 25 from individuals with normal hearts and 133 from patients known to have other types of organic heart disease.

2. It was found that patients with coronary sclerosis showed abnormalities in Lead IV more often than any of the control groups.

3. The abnormalities in Lead IV in the patients with coronary sclerosis were almost always associated with abnormal findings in the conventional 3 leads, but the deviations were usually more striking in Lead IV.

4. Patients with coronary sclerosis having clinical evidence of myocardial incompetence showed abnormalities in Lead IV more often than patients without such myocardial incompetence.

5. The 4 major types of abnormal Lead IV found in patients with coronary sclerosis are described. They are the positive Q–R–S_4 type (the most common), the negative Q–R–S_4 type, the positive and diphasic T_4 type and the deeply negative T_4 type.

6. The value of Lead IV in determining the status of the coronary circulation was confirmed by postmortem examination in 7 cases of coronary sclerosis.

7. Serial 4-lead electrocardiograms were obtained in 56 of the 200 patients with coronary sclerosis covering a period of from 4 months to 2 years or more. Analysis of these records and, in addition, those obtained on patients with recent coronary occlusion and other conditions showed the value of serial electrocardiograms in evaluating the state of the coronary circulation. This is particularly important because of the paucity of precise clinical evidence in a large number of such patients.

8. If records obtained in patients suffering from acute infectious processes, those taken on moribund patients, and those due to large doses of digitalis are excluded, then one can determine from serial 4-lead electrocardiograms whether the coronary insufficiency is: (1) An acute transitory coronary insufficiency, *i. e.*, angina pectoris, nocturnal dyspnea, cardiac asthma, or its equivalent; (2) a subacute coronary insufficiency, *i. e.*, recent occlusion, thrombotic or arteriosclerotic, with myocardial infarction; (3) a chronic non-progressive coronary insufficiency; or (4) a chronic progressive coronary insufficiency. This functional classification should prove as useful in evaluating the clinical course of the patients as the anatomic and etiologic classifications.

9. This study emphasizes the importance of taking serial 4-lead electrocardiograms in all patients suspected of having coronary disease in estimating the degree of insufficiency of the coronary circulation and the rate of its progress.

We are indebted to Dr. P. Markle for technical assistance, and to the Medical Staff of the Hospital for permission to use the records of their private patients in this study.

REFERENCES.

1. Gilchrist, A. R., and Ritchie, W. T.: Quart. J. Med., **23**, 273, 1930.
2. Wilson, F. N., MacLeod, A. G., Barker, P. S., Johnston, F. D., and Klostermyer, L. L.: Heart, **16**, 155, 1933.
3. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Am. Heart J. (in press).
4. Wolferth, C. C., and Wood, F. C.: Am. J. Med. Sci., **183**, 30, 1932.
5. Katz, L. N., and Kissin, M.: Am. Heart J., **8**, 595, 1933.
6. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Arch. Int. Med., **52**, 752, 1933.
7. Wilson, F. N.: Am. Heart J., **5**, 599, 1930.
8. Katz, L. N., and Bohning, A.: (Unpublished).
9. Masters, A. H.: Am. Heart J., **9**, 511, 1934.
10. Goldbloom, A.: Am. J. Med. Sci., **187**, 489, 1934.
11. Katz, L. N., and Johnson, V.: Elements of Electrocardiographic Interpretation, Chicago, Univ. of Chicago Press, 1932.
12. Parkinson, J., and Bedford, D. E.: Heart, **14**, 195, 1928.
13. Hoffman, A. M., and Delong, E.: Arch. Int. Med., **51**, 947, 1933.
14. Wilson, F. N., Johnston, F. D., Hill, I. G. W., MacLeod, A. G., and Barker, P. S.: Am. Heart J., **9**, 459, 1934. Wilson, F. N., Johnston, F. D., and Barker, P. S.: Ibid., p. 472.
15. Nichol, A. D.: Ibid., p. 72, 1933.
16. Wolferth, C. C., Margolies, A., and Bellet, S.: Trans. Assn. Am. Phys., **48**, 187, 1933.
17. Katz, L. N., Landt, H., and Bohning, A.: Am. Heart J. (in press).
18. Katz, L. N., Saphir, O., and Strauss, H.: Ibid. (in press).
19. Strauss, H., and Katz, L. N.: Ibid. (in press).
20. Katz, L. N., and Landt, H.: Am. J. Med. Sci (in press).
21. Katz, L. N.: Am. Heart J. (in press).
22. Korey, H., and Katz, L. N.: Am. J. Med. Sci., **188**, 387, 1934.
23. Katz, L. N.: Physiol. Rev., **8**, 447, 1928.
24. Lieberson, A. M., and Liberson, F.: Ann. Int. Med., **6**, 1315, 1933.

CORONARY THROMBOSIS AND ITS EFFECT ON THE SIZE OF THE HEART.

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Although it has been recognized for many years that arteriosclerosis of the peripheral vessels does not *per se* cause cardiac enlargement, statements are made that coronary artery disease results in an increased weight of the heart.[1,2,3,4] Others believe that some extra coronary mechanism is responsible for cardiac hypertrophy found in persons with coronary disease.[5,6,7] Prolonged exercise, following experimental cardiac infarction in dogs, does not result in cardiac hypertrophy.[8]

There has not been published a follow-up study of patients with coronary occlusion who had a normal sized heart at the time of the

occlusion to determine whether cardiac hypertrophy ensued. This report is such a study. A total of 20 cases was followed. All had definite clinical and electrocardiographic evidence of an acute coronary obstruction. Fluoroscopic or orthodiagraphic examination revealed in every case a normal sized heart. The examinations were made by one or both of us. All the patients were males. The ages were from 30 to 76 years. The average time from the first to the last Roentgen examination was $3\frac{5}{6}$ years. The shortest was 5 months, the longest 9 years and 10 months. In many of the cases repeated interim Roentgen ray examinations were made. In no instance was there found any increase in the size of the heart. Aneurysm and acute dilatation of the heart which occasionally follow coronary thrombosis and which might simulate cardiac hypertrophy were not encountered. Three of the patients are dead. Autopsy in 1 case 5 months after the coronary accident confirmed the clinical diagnosis. Table 1 is a summary of the data.

TABLE 1.—ANALYSIS OF 20 CASES SHOWING NORMAL HEART SIZE AFTER CORONARY OCCLUSION.*

Case No.	Age.	Initial Roentgen ray. Date.	Initial Roentgen ray. Size of heart.	Final Roentgen ray. Date.	Final Roentgen ray. Size of heart.
1	51	Aug. 13, 1928	Normal	May 4, 1934	Normal
2	58	March 17, 1927	Normal	Feb. 16, 1934	Normal
3	30	June 1, 1925	Normal	June 8, 1934	Normal
4	58	Jan. 11, 1926	Normal	Feb. 18, 1930	Normal
5	50	Feb. 23, 1932	Normal	May 25, 1934	Normal
6	44	June 18, 1932	Normal	May 26, 1934	Normal
7	42	March 4, 1924	Normal	Jan. 8, 1934	Normal
8	48	Oct. 10, 1931	Normal	Dec. 30, 1932	Normal
9	66	Oct. 7, 1931	Normal	July 7, 1933	Normal
10	64	Feb. 24, 1932	Normal	July 7, 1932	Normal
11	45	Oct. 5, 1927	Normal	Feb. 8, 1932	Normal
12	41	Oct. 6, 1926	Normal	June 15, 1929	Normal
13	47	June 1, 1933	Normal	June 7, 1934	Normal
14	58	Sept. 6, 1928	Normal	Feb. 12, 1932	Normal
15	55	Aug. 1, 1931	Normal	May 14, 1934	Normal
16	61	July 23, 1928	Normal	Feb. 18, 1931	Normal
17	42	June 7, 1928	Normal	April 16, 1929	Normal
18	53	June 26, 1931	Normal	June 8, 1934	Normal
19	49	March 6, 1925	Normal	May 25, 1934	Normal
20	76	Nov. 1, 1932	Normal	May 28, 1934	Normal

* All males.

Comment. In any discussion of the cause of cardiac hypertrophy in a patient without an elevated blood pressure a pre-existing hypertension which could cause the cardiac enlargement must be excluded. Such a possibility has not always been considered and probably accounts for the confusion in the literature as to the association of coronary disease and cardiac hypertrophy. Even though the former level of the blood pressure is unknown, clinical or pathological evidence of an antecedent hypertension should be sought for. Aside from the cardiac hypertrophy, which of itself may be proof

of a former hypertension, these patients may show impairment of renal function or uremia, a roentgenologic cardiac silhouette suggesting hypertension, coronary types of electrocardiograms as are so often found in known hypertensive individuals, ophthalmoscopic signs of a previous hypertensive state, arteriolar sclerosis of the voluntary muscles as observed in biopsy specimens, and finally autopsy may disclose arteriolar lesions which always evidence a persistent hypertension during the life of the individual.[9]

Summary. Twenty patients who had a normal sized heart at the time they experienced a coronary thrombosis did not develop roentgenologic evidence of cardiac enlargement although they were observed from 5 months to $9\frac{5}{6}$ years.

REFERENCES.

1. Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurysm, Heart, **10**, 301, 1923.

2. Parkinson, J., and Bedford, E.: Cardiac Infarction and Coronary Thrombosis, Lancet, **1**, 4, 1928.

3. White, P. D.: Heart Disease, New York, The Macmillan Company, p. 455, 1931.

4. Bartels, E. C., and Smith, H. L.: Gross Cardiac Hypertrophy in Myocardial Infarction, Am J. Med. Sci., **184**, 452, 1932.

5. Miller, H. R., and Weiss, M. M.: Disease of the Coronary Arteries: Its Occurrence Without Gross Cardiac Hypertrophy, Arch. Int. Med., **42**, 74, 1928.

6. Jones, E. W.: A Radiographic Study of the Coronary Arteries in Health and Disease, Quart. J. Med., **24**, 199, 1931.

7. Nathanson, M. H.: Disease of the Coronary Arteries, Clinical and Pathological Features, Am. J. Med. Sci., **170**, 240, 1925.

8. Sutton, D. C., and Davis, M. D.: Effects of Exercise on Experimental Cardiac Infarction, Arch. Int. Med., **48**, 1118, 1931.

9. Horine, E. F., and Weiss, M. M.: The Diagnosis of Hypertensive Heart Disease in the Non-hypertensive Stage (To be published).

BOOK REVIEWS AND NOTICES

SURGICAL DISEASES OF THE CHEST. By EVARTS AMBROSE GRAHAM, A.B., M.D., F.A.C.S., Professor of Surgery, Washington University School of Medicine, St. Louis; Surgeon-in-Chief, Barnes Hospital and St. Louis Children's Hospital, etc.; JACOB JESSE SINGER, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician, Barnes Hospital, etc., and HARRY C. BALLON, M.D., C.M., F.A.C.S., Formerly Assistant Professor of Surgery, Washington University School of Medicine; Formerly Assistant Surgeon, Barnes Hospital. Pp. 1070; 637 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $15.00.

IT is difficult to do adequate justice to this volume. Within 1070 pages the authors have thoroughly covered the surgical lesions of the chest. The subject matter is delightfully presented, adequately discussed and brings to the reader the wealth of the author's knowledge of the subject. The illustrations are well done and clearly bring out the points for which they are intended. Special chapters have been contributed by Ray W. Matson, Helen Lamb, David H. Ballon and Ralph C. Matson. There are 22 chapters beginning with a brief discussion of "Some Physiological Considerations of Importance to the Thoracic Surgeon" and ending with a presentation of the senior author's chest service at the Barnes Hospital.

The Table of Contents leaves nothing to be desired. This work is more than a thoracic surgery, for it covers the medical aspects of thoracic lesions which have a surgical significance just as carefully as it does the surgical technique. The lesions of the thoracic cage, pleura, lungs and bronchi, mediastinum, pericardium, heart, esophagus and diaphragm are adequately presented. Anesthesia, bronchography and bronchoscopy and pneumolysis are thoroughly reviewed.

Truly here is a work which every surgeon must have in his library and which most internists will do well to possess. Within its field it occupies a preëminent position. I. R.

DIABETES MELLITUS AND OBESITY. By GARFIELD G. DUNCAN, M.D., C.M. (MCGILL), Associate in Medicine in the Jefferson Medical College, Philadelphia; Assistant Physician to the Pennsylvania Hospital, etc. With an introduction by THOMAS MCCRAE, M.D., Professor of Medicine in the Jefferson Medical College, etc. Pp. 215; 9 illustrations and 40 tables. Philadelphia: Lea & Febiger, 1935. Price, $2.75.

THE book contains chapters on the etiology, incidence and pathology of diabetes; on food and food metabolism which present the practical physiology; symptoms and diagnosis; diabetes in children; the prevention and treatment of diabetes, and on its complications. There is a chapter on the clinic and ward routine for diabetics and one on laboratory methods. The section on obesity comprises four short chapters. There is the usual appendix of food values and average weight tables.

It is apparent from this that the author is presenting the subject in textbook outline and for physicians. The material is of textbook caliber and the whole book is exceptionally well written with a directness and clarity that could hardly be improved. There is relatively little bibliography and no attempt is made to present the complex medical ideas in the field of

metabolism. The chapter on clinic and ward routines for the diabetic with and without various complications will be welcomed by the practitioner who wishes exact directions rather than principles. The section on obesity is simple, sufficiently resourceful and wisely avoids all fads. The book as a whole is a manual of diabetes and obesity for the physician, most of which is in language that he can use in the instruction of his patient, and should be of very real value to the practitioner. F. L.

ATLAS FUNDUS OCULI. By WILLIAM HOLLAND WILMER, M.D. (University of Virginia), LL.D. (Georgetown University), Sc.D. (Princeton and New York Universities), Professor of Ophthalmology and Director of the Department of Ophthalmology of the Johns Hopkins University School of Medicine; Ophthalmologist-in-Chief to the Johns Hopkins Hospital, etc. Introduction by WARFIELD T. LONGCOPE, M.D., Professor of Medicine and Director of the Department of Medicine of the Johns Hopkins School of Medicine, Pp. 100; 100 colored plates. New York: The Macmillan Company, 1934. Price, $35.00.

MEDICAL atlases are among the more enduring forms of memorials, as Baillie, Hope, Carswell and Cruveilhier testify, to consider the field of pathology alone. What more fitting than that a leader in his specialty should cap the climax of his active career with such a splendid monument to his own and to American ophthalmological achievement! But, as we have been told on good authority, this particular atlas is even more important as ranking at the very top in the important field of study of the eye grounds. After 13 plates of normal human and animal fundi, various pathologic conditions are portrayed. Among the more conspicuous are anomalies (6), atrophies (4), choroido-retinitis (19), arteriosclerosis (8), changes in blood diseases (6), neoplasma (5).

As pointed out by Dr. Longcope in the introduction, the Atlas derives its value from several sources: "In the first place, it may be regarded as a series of personal records, selected by Dr. Wilmer with the discretion and wisdom that comes with great experience, to illustrate the appearance of the fundus under normal conditions and in a great variety of pathologic states; in the second place, it furnishes through the histories, so excellently epitomized, the information necessary for a useful correlation of the pathologic lesions in the fundus with the disease from which the patient suffered; and in the third place, it unfolds before our eyes one beautiful reproduction after another, each one of which depicts the changes in the fundus with a brillancy and accuracy that cannot be surpassed." Many years in the making—as may be seen from the various dates on the plates—with an obviously close coöperation between a competent artist and a clinician of wide experience working with extensive material, these beautiful, accurate, colored reproductions should stand as the court of last resort for many years. Colored photography will indeed have to go far before it can surpass this magnificent achievement. E. K.

THE DANGEROUS AGE IN MEN. A Treatise on the Prostate Gland. By CHESTER T. STONE, M.D., Clinical Assistant Surgeon, Urological Division, Bellevue Hospital, New York City; Urologist, Bergen County Hospital, Oradell, N. J.; Consultant Urologist, Rome State School, Rome, N. Y. Pp. 105. New York: The Macmillan Company, 1935. Price, $1.75.

THE copy of this book that we received for review is one of the fourth printing since last July, and this is not surprising with its provocative title,

and chapter headings such as "When is a Man Old?" "A Word to the Wives," and so on. Even in the opening chapter, the conservative physician's antagonism is aroused by such statements as: "Medical authors have variously estimated that from 35 to 90% of all adult males have trouble with the prostate gland," "It is, therefore, the most important of the sexual organs," "Since without sexual power there can be no real bodily and mental strength or capacity, this power must be kept in a state of efficiency by the regular and proper exercise of the sexual function," "No organ in the human body can properly function without the stimulating aid of the internal secretion from the sex glands." Later, referring to an active sex life interrupted by continence, "Unless this patient again establishes his sexual life, or goes to a urologist for proper massage and treatment, he is sure of a prostatitis." Even in a book written for the laity, are such categorical statements justified or even expedient? Good advice is given, to be sure, about moderate exercise, diet and sleep, psychic and physical harmony and the need for medical advice; but these, we believe, are more than balanced by the unguarded presentations of half knowledge that are capable of causing much damage. E. K.

THE CYCLOPEDIA OF MEDICINE. INDEX TO VOLUMES 1 TO 12. GEORGE MORRIS PIERSOL, Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS I. LEDERER, B.S., M.D., A. GRAEME MITCHELL, M.D. Pp. 415. Philadelphia: F. A. Davis Company, 1934. Price, $120.00 for the set.

ALTHOUGH the topics discussed in the twelve volumes of the Cyclopedia of Medicine are arranged alphabetically, the material is so voluminous, and its arrangement of a necessity at times arbitrary, that the usefulness of the Cyclopedia depends in no small measure upon an adequate index. This need is fully met in the volume which has just appeared. The setting in bold-faced type of all references to treatment is a distinct advantage. R. K.

FRENCH MEDICINE. Volume 15 of Clio Medica. By M. LAIGNEL-LAVASTINE, Professor in the Medical Faculty in Paris; Secretary-General of the International Society of Medical History, and M. RAYMOND MOLINERY, Gold Medalist of the Academy of Medicine; Member of the French Society of Medical History. Translated by E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania. Pp. 187; 14 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $2.50.

To the Clio Medica series has been contributed a delightful little book on the history of medicine in France. Included subjects, described in interesting manner, are the curative magic of remote times, the primitive surgery of the Romans, the ecclesiastic origin of medical teaching and the strange plagues of the middle ages. The reader learns that the waters of the famous French Spas were recognized for their medicinal value in the earliest Gallo-Roman period, when great thermal stations were established. An account is given of the long succession of inspired pioneers in medicine—Lanfranc, Albertus Magnus, Bichat, Fernel, Paré, Laennec, Pasteur and many others whose work culminated in making Paris the center of the medical world of the 19th century. The book is very complete and suffers only from the brevity of description necessitated by so broad a subject. L. L.

DIE WERKE DES HIPPOKRATES. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STRICKER, Würzburg. Regimen: Books 1 and 2 (Part 3, Price, Rm. 2.50); Books 3 and 4 (or Dreams), Regimen of Health (Part 4, Price, Rm. 2.10). Pp. Part 3, 98; Part 4, 80. Stuttgart: Hippokrates-Verlag G. M. B. H., 1934. (To be published in 25 parts costing ca. Rm. 100, card binding.)

IN the sense that in these 5 books the author offers a complex survey of the nature of man, they might be regarded as forming the very center of Hippocratic doctrine. Everything human is governed by natural law; health must be obtained by obeying these laws; disease results from a marked departure from them. The Regimen represents Hippocrates' "discovery" of how to regulate food and health so that health may be obtained; or disease, if present, be combated. This is indeed a great step beyond demonic pathology and magic treatment. The Regimen has a strong philosophic trend: far from holding close to observation, it makes free use of the imagination with a carefree disregard of truth of detail, so long as a truthful impression of the whole is conveyed.

These books are also characteristic of much of the Corpus, in that they are not definitely from the hand of Hippocrates himself—they are not even mentioned by Erotian, for instance. They have been divided by different scribes in different ways, an occurrence which accounts for the book on Dreams appearing as Book 4 of the Regimen; sometimes it was included without any separate title at all. Littré has one series of chapters for all four books. The weaknesses arising from detailing factual statements from a basis of unproved hypothesis are only too often apparent. Book 4 offers a detailed—and, of course, fanciful—explanation of the significance of dreams and the influence of heaven, of the earth and of the dead in their production.

In this edition, the interesting forewords and lists of contents that accompany each section are all the more valuable, as no index is as yet available.

E. K.

PRACTICAL NEUROLOGICAL DIAGNOSIS. With Special Reference to the Problems of Neurosurgery. By R. GLEN SPURLING, M.D., Assistant Clinical Professor of Surgery, in charge of neurosurgery, University of Louisville School of Medicine. Pp. 233; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

STUDENTS and practitioners are offered this book of diagnostic principles as an aid to the earlier recognition of surgical lesions. Much space is given to the neurologic examination, including a study of the cranial nerves, the cerebrum, the cerebellum, the spinal cord and the reflexes. A section on spinal fluid ends with elaborate tables showing the findings in health and disease, and in spinal subarachnoid block. The final section considers Roentgen ray diagnosis of the skull and spine, together with methods for obtaining encephalograms, ventriculograms and lipiodol investigations of the spinal cord. Many pertinent photographs aid in the interpretations.

N. Y.

FRACASTORO. SYPHILIS OR THE FRENCH DISEASE. A Poem in Latin Hexameters. By GIROLAMO FRACASTORO. With a Translation, Notes and Appendix by HENEAGE WYNNE-FINCH, M.A. (OXON.), and an Introduction by JAMES JOHNSTON ABRAHAM, C.B.E., D.S.O., M.A., M.D. (DUB.), F.R.C.S. Pp. 253; illustrated. London: William Heinemann, Ltd., 1935. Price, 10/6.

WE welcome this latest edition to Fracastorius literature. A well chosen Introduction (38 pages) gives even those readers who have no previous

knowledge of the subject a good background of the views of the origin of syphilis and its remarkable spread through Europe at the end of the 15th century, of the use of mercury and guaiac, of the word "syphilis," with details of Fracastoro's life and the high lights of the subsequent history of syphilis. The Translator's note includes an interesting bit of bibliographic detective work, namely, Fulton's discovery in the Bibliothèque Nationale's copy of a note in Fracastoro's own hand as to the two debatable lines which were added in his handwriting in that copy, but only occasionally included in texts: The prose translation aims to reproduce the author's meaning accurately and yet retain as far as possible the grace and charm of the original—the goal of every translator worth his salt. On the former of these points we are not competent to express an opinion; the latter has been achieved as well as the flowery, circumlocutory style of the 16th century will readily permit. The rather copious notes, footnotes and in the appendices, are unobtrusive helps to further understanding. E. K.

MARTINI'S PRINCIPLES AND PRACTICE OF PHYSICAL DIAGNOSIS. Edited by ROBERT F. LOEB, M.D., Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University, and Presbyterian Hospital, New York. From the authorized translation by GEORGE J. FARBER, M.D. Pp. 213; 30 illustrations. Philadelphia: J. B. Lippincott Company, 1935. Price, $2.00.

"OUR first problem is to indicate the ways and means by which the physician may use his senses for the recognition and evaluation of disease. In this attempt the mention of the more important signs and to some extent also their arrangement will be a valuable and essential means to to this end. . . . . Innumerable newly developed diagnostic procedures have been described during the last decades. Yet the simpler method of the practising physician have remained the same. This book is devoted to the physical methods of the latter." (From the Author's Preface.)

PHYSIOLOGY IN MODERN MEDICINE. By J. J. R. MACLEOD, M.B., LL.D., D.Sc., F.R.C.P., F.R.S., Regius Professor of Physiology in the University of Aberdeen, Scotland, etc. Assisted in the present edition by PHILIP BARD, Professor of Physiology, Johns Hopkins University School of Medicine, EDWARD P. CARTER, Adjunct Professor of Medicine, Johns Hopkins University and Associate Physician, Johns Hopkins Hospital, N. M. D. OLMSTED, Professor of Physiology, University of California, J. M. PETERSON, Lecturer in Experimental Physiology, University of Aberdeen, and N. B. TAYLOR, Professor of Physiology, University of Toronto. Pp. 1154; 297 illustrations, including 7 plates in colors. Seventh edition. St. Louis: The C. V. Mosby Company, 1935. Price, $8.50.

IT is to be hoped that the recent death of the author of this well-known work will not prevent its continuation in future editions as one of the standard texts on physiology in English-speaking countries. Among the five assistants in the preparation of this edition there is surely sufficient talent to ensure the adequacy of future revisions. The book at last takes its proper status by omitting "Biochemistry" from its title. There have been slight modifications throughout, the chief improvements being the revision by Bard of the chapter on Neuromuscular Mechanisms, and the assembling of the revised bibliography at the end of the volume instead of each section. E. K.

BLOOD GROUPS AND BLOOD TRANSFUSION. By ALEXANDER S. WIENER, A.B., M.D. Pp. 220; 41 illustrations and 72 tables. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

To Bernheim's, Feinblatt's and Snyder's books on this subject is now added a work by one who has himself contributed notably to the knowledge of the problem involved. This work, adequately but not exhaustively documented, presents in 18 chapters such topics as the history of, indications for and technique of blood transfusion, the four blood groups with the various nomenclatures and the newer subgroups, and a rather full discussion of the genetic factors involved. It closes with chapters on relation of blood groups to clinical medicine and other medicolegal applications. It will be a useful aid to anyone wishing an authoritative statement of the subject in its latest developments. E. K.

DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., SC.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas, School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.P.C.P. (EDIN.), Assistant in Dermatology, University of Kansas, School of Medicine. Pp. 1433; 1310 illustrations and 11 colored plates. Ninth edition, revised and enlarged. St. Louis: The C. V. Mosby Company, 1935. Price, $12.50.

THIS ninth edition in 20 years of a deservedly popular work, revised and enlarged, reflects the continuous expansion of dermatologic studies and publications. Some two score new conditions are here described for the first time. A notable feature, in this as in other recent Mosby books, is the water-proof, vermin-proof cloth binding in which the text is enclosed. E. K.

THE CARE OF THE AGED, THE DYING AND THE DEAD. By ALFRED WORCESTER, M.D., SC.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 77. Springfield, Ill.: Charles C Thomas, 1935. Price, $1.00.

THIS little book with the big title was written especially to interest younger medical practitioners in one phase of the art of medical practice. There is a chapter on each of the three divisions of the title. In the care of the aged the physician is urged to devote more attention to the patient's comfort and less time to efforts at impossible rejuvenation. There are many interesting suggestions for the tactful handling of patients. The advice on diet and care of the demented is of special note. There is practically no mention of drugs. Several questionable broad statements are made, such as, "in the prevention of suffering, prostatectomy, for instance, is second only to the discovery of anæsthetics." While the information is more or less general it is none the less interesting. The average physician probably devotes too much thought to the scientific treatment of his patients, young as well as old, and too little attention to their actual comfort.

The chapter on the care of the dying shows the author's unusual and sympathetic understanding of the very last comforts of the patient.

In the care of the dead we see the folly of elaborate and expensive burials and the injustice to future generations by our present sequestrations of land for graveyards.

While this is not a treatise on scientific medicine it is nevertheless an an entertaining and instructive book for physicians, and has the advantage of brevity. N. B.

USEFUL DRUGS. A List of Drugs Selected to Supply the Demand for a Less Extensive Materia Medica, with a Brief Discussion of Their Actions, Uses and Dosage. Edited by ROBERT A. HATCHER, PH.M., SC.D., M.D., and CARY EGGLESTON, M.D. Prepared under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association. Pp. 203. Ninth edition. Chicago: American Medical Association, 1934. Price, 60 cents.

"THIS book represents a valuable and increasingly effective phase of the efforts of the Council on Pharmacy and Chemistry on behalf of rational therapeutics. Since its first appearance, in 1913, it has become a recognized work in its field. It has been adopted as a textbook by teachers of therapeutics in the best medical schools and by various examining and licensing boards. The various editions and revisions since that time have been undertaken in the effort to keep it abreast with the advance of therapeutics. Drugs that have become obsolete have been deleted, and others the value of which has become established have been added. The statement of actions, uses and dosage of the various drugs are revised after discussion by the whole Council. They represent the latest and best results of therapeutics and pharmacologic revision." (From Review in *J. Am. Med. Assn.*)

JOURNAL OF TECHNICAL METHODS AND BULLETIN OF THE INTERNATIONAL ASSOCIATION OF MEDICAL MUSEUMS, No. XIV. Edited by MAUDE E. ABBOTT, M.D., McGill University, Montreal. Editorial Board: WILLIAM BOYD, Winnipeg, Man.: VICTOR C. JACOBSEN and ROBERT A. MOORE, New York City; CARL V. WELLER, Ann Arbor, Mich. Pp. 134; 30 illustrations. Montreal: The Medical Museum, McGill University, 1935. Price, $2.00.

THIS journal contains too many articles of interest to make selective comment possible or desirable. Turning from the pithy editorials to the original communications, the morphologist is equally "intrigued" by the articles on museum administration and technique, photographic and microscopic technique, and the six short articles on various types of cardiovascular anomalies. Would that circumstances permitted a more extensive presentation at more frequent intervals! E. K.

METHODS OF TREATMENT. By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, Kansas City General Hospital, etc. With chapters on special subjects by H. C. ANDERSSON, M.D., URSULLA BRUNNER, R.N., J. B. COWHERD, M.D., PAUL GEMPEL, M.D., H. P. KUHN, M.D., CARL O. RICHTER, M.G., F. C. NEFF, M.D., E. H. SKINNER, M.D., E. R. DEWEESE, M.D., and O. R. WITHERS, M.D. Pp. 879; 102 illustrations. Fifth edition. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

"THIS book was planned to furnish an outline of all the methods of treatment in internal medicine. Its design contemplates gathering together material otherwise widely scattered in medical literature, as, for instance, descriptions of the technic of spinal puncture, blood transfusion, the wet pack and the ketogenic diet. In the sections on treatment in texts on the practice of medicine a method is recommended usually without any instructions as to technic, usually, indeed, without any discussion of the rationale behind it. Texts on therapeutics and pharmacology are usually devoted

exclusively to drugs. Here all therapeutic procedure is brought together within the compass of one volume. . . . . A word concerning the arrangement of the material may be helpful. The first part describes each procedure under the heading of drugs, diet, hydrotherapy, etc. The second considers the application, the results to be expected, etc., under the heading of the various diseases. The advantage of the arrangement is the lack of necessity for repetition. Thus in Part I the action of digitalis dosage, preparations, etc., are set down. In Part II whenever digitalis is indicated or contraindicated, in heart failure, pneumonia, thyrotoxicosis, etc., it is necessary to refer only to the description in Part I in each case." (From Author's Preface.)

THE 1934 YEAR BOOK OF PEDIATRICS. Edited by ISAAC A. ABT, D. Sc., M.D., Professor of Pediatrics, Northwestern University Medical School; Attending Physician, Passavant Hospital, etc. With the collaboration of ARTHUR F. ABT, B.S., M.D., Associate in Pediatrics, Northwestern University Medical School; Adjunct Attending Pediatrician, Michael Reese Hospital, etc. Pp. 541; 74 illustrations. Chicago: The Year Book Publishers, Inc., 1935. Price, $2.25.

IT is difficult to present a fair review of a volume which presents in such compact form a great variety of material. In general, one can say that the editor and his collaborator has covered the year's output of pediatric literature completely. They have made a good selection of material, abstracts of which convey enough information to satisfy the average reader. Some of the abstracts of more thought provoking papers will influence the industrious reader to seek the original articles. In the main, those papers which presented research work of an ultrascientific nature have been slighted and no attempt has been made to choose material from the literature of the fundamental sciences which might have later significance in pediatrics.

However, the volume should be of great value to the busy practitioner who desires accurate, readable abstracts of the recent literature in this field. E. T., JR.

DOCTORS AND JURIES. The Essentials of Medical Jurisprudence. By HUMPHREYS SPRINGSTUN of the Detroit Bar. Pp. 155. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $2.00.

AMERICAN books on legal medicine are sparse, and British law varies from ours considerably. This small and inexpensive book, designed by a lawyer for doctors, lawyers and others wanting knowledge of the relations of law to medicine should fill a gap. The 18 brief chapters cover such topics as contracts, negligence, damages, burden of proof, testimony, insanity and so on. E. K.

KLINIK DER ERKRANKUNGEN DES HERZMUSKELS. X. Fortbildungs-Lehrgang in Bad-Nauheim. 20–23 September, 1934. Herausgegeben von der Vereinigung der Bad-Nauheimer Arzte. Pp. 170; 63 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 70.

SINCE 1920 these volumes have been presenting, almost annually, articles by leaders in their profession on various phases of heart disease. The previous volumes have been on such general topics as Treatment of Cardiac Insufficiency, Modern Methods of Diagnosis, Hypertension, the Arrhythmias, Cardiac Neuroses—all with considerable emphasis on treatment. The present volume treats of myocardial disease from the points of view of anatomy, electrocardiography, radiology, clinical pictures and treatment. Aschoff's articles on myocardial disease not the result of vascular lesions and Hochrein's on cardiac circulation and cardiac pain should prove of especial interest to many. E. K.

THE 1934 YEAR BOOK OF OBSTETRICS AND GYNECOLOGY. *Obstetrics.* Edited by JOSEPH B. DE LEE, A.M., M.D., Professor of Obstetrics, University of Chicago Medical School, etc. *Gynecology.* Edited by J. P. GREENHILL, B.S., M.D., F.A.C.S., Associate Professor of Gynecology, Loyola University Medical School; Professor of Gynecology, Cook County Graduate School of Medicine. Pp. 717; 96 illustrations. Chicago: The Year Book Publishers, Inc., 1935. Price, $2.50.

FOR those who wish to keep abreast of the most important obstetrical and gynecological literature this edition offers a splendidly prepared digest of the subject in American and foreign journals.

The obstetrical division has been prepared by De Lee for the thirtieth time. His frequent comments, terse, pungent, and at times caustically critical, add a piquantly personal sauce to many of the abstracts.

Greenhill has carefully reviewed the gynecological literature. There is no chaff here, and again the comments serve to emphasize the worth of the original articles.

The volume containing references to 652 articles and reproducing 96 illustrations from the original texts forms an indispensable aid to both teacher and practitioner. P. W.

RATS, LICE AND HISTORY. Being a Study in Biography, Which After Twelve Preliminary Chapters Indispensable for the Preparation of the Lay Reader, Deals with the Life History of Typhus Fever. By HANS ZINSSER. Pp. 301. Boston: Little, Brown & Co., 1935. Price, $2.75.

IT must be said at the beginning that the title of this book would read more properly, "Rats, Lice, History and Dr. Hans Zinsser." It is, in effect, not the "biography" of typhus which it claims (with tongue in cheek) to be, but the apocalypse of an ebullient scientist whose mental and emotional horizon reaches far beyond the walls of his laboratory. Were there an index to the book, which most unfortunately there is not, omitted supposedly as a *beau geste* to the layman for whom the book is primarily intended, it would be found to contain an array of names, pertinent and impertinent (Aristotle—Stein, Gertrude), which would do credit to the omniscient daily book-reviewer of the New York *Times*. The variety of grist required by Dr. Zinsser's mill is, if we may be permitted a contemporary term of understatement, colossal.

The book is, more or less frankly, a thoroughly successful exercise in the current vein of "popular science" writing, not unrelated to similar, and highly popular, works by certain of the author's colleagues, works toward which he, unfortunately under the circumstances, permits himself a derisive gesture. As such, it has much indeed to offer the *homo incognitus* for whom it is intended. Its historical information on typhus is derived not only from the most eminent authorities (to whom credit is scrupulously given, and given, from a literary standpoint, with considerable adroitness), but in many cases from the author's own recourse to original sources. The information, moreover, is frequently of poignant interest. And it is not likely that on the author's own ground—the technical elucidation of the typhus virus, its etiology, and habits—anyone will be tempted to question Dr. Zinsser's right to speak with the voice of authority.

The book is philosophically discursive in the grand manner of Sterne and Melville and others of the elect. Its greatest appeal will be to those fortunate enough to capture from its somewhat determined roguishness the same mental stimulation and zest which undoubtedly went into the writing of it. They will unquestionably be many and not at all disturbed, rightly, by the remaining few who still deem it a hopeful symptom of maturity, generally speaking, to count ten. W. McD., 2d.

NEW BOOKS.

Journal of Technical Methods and Bulletin of the International Association of Medical Museums, No. XIV. Edited by MAUDE E. ABBOTT, M.D., McGill University, Montreal. Editorial Board: WILLIAM BOYD, Winnipeg, Man.; VICTOR C. JACOBSEN and ROBERT A. MOORE, New York City; CARL V. WELLER, Ann Arbor. Pp. 134; 30 illustrations. Montreal: The Medical Museum, McGill University, 1935. Price, $2.00. (Review, p. 867.)

Le Nodule de la Corde Vocale. By JEAN TARNEAUD, Oto-Rhino-Laryngologiste de l'Hôpital Bellan et du Conservatoire national de Musique de Paris. Pp. 139; 24 illustrations. Paris: Norbert Maloine, 1935. Price, 30 fr.

Names of Surgical Operations. Compiled and Arranged by the Western Surgical Association Through Its Special Committee. Edited by CARL E. BLACK, A.M., M.D., Jacksonville, Ill. Pp. 102. St. Paul, Minn.: Bruce Publishing Company, 1935. Price, $3.00.

"The work of the Committee of the Western Surgical Association in the preparation of a standard nomenclature for surgical operations represents an enormous amount of painstaking labor and will prove of the greatest assistance to all hospital record librarians, as well as to the surgeons who are obliged to use hospital records for the collective study of clinical material. It is perhaps to be regretted that the identification of certain standard operations by the names of their originators must be abandoned in favor of the anatomic term describing the procedure employed, but the sentimental objection must give way to the practical point of accuracy." (From Dr. Greenough's Foreword.)

Das Extremitäten-, Thorax- und Partial-Elektrokardiogramm des Menschen. Eine Vergleichende Studie. By PROF. DR. FRANZ MAXIMILIAN GROEDEL, Direktor des William C. Kerckhoff-Herzforschungs-Instituts zu Bad-Nauheim. Band 1: Text (358 pages; 334 illustrations); Band 2: Atlas with 200 plates. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 25.

Klinik der Erkrankungen des Herzmuskels. X. Fortbildungs-Lehrgang in Bad-Nauheim. 20.–23. September, 1934. Herausgegeben von der Vereinigung der Bad-Nauheimer Ärzte. Pp. 170; 63 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 70. (Review, p. 868.)

Koronarinfarkt und Koronarinsuffizienz. In Vergleichender Elektrokardiographischer und Morphologischer Untersuchung. By PROF. DR. MED. FRANZ BÜCHNER, Vorstand des Pathologischen Instituts am Horst-Wessel-Krankenhaus der Stadt Berlin, PROF. DR. MED. ARTHUR WEBER, Vorstand des Balneologischen Universitätsinstituts in Bad-Nauheim, and DR. MED. BERTHOLD HAAGER, Assistent am Balneologischen Universitätsinstitut in Bad-Nauheim. Pp. 104; 116 illustrations. Leipzig: Georg Thieme, 1935. Price, Rm. 15.

A Suggestion for an Experimental Trial of Alum-treated Formalized Virus in the Active Local and General Immunization Against Poliomyelitis. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 11. Cleveland: Mount Printing Company, 1935. (Price not given.)

Doctors and Juries. The Essentials of Medical Jurisprudence. By HUMPHREYS SPRINGSTUN of the Detroit Bar. Pp. 155. Philadelphia: P. Blakiston's Son & Co., 1935. Price, $2.00. (Review, p. 868.)

A Textbook of Biochemistry. Edited by BENJAMIN HARROW, PH.D., Associate Professor of Chemistry, The City College, College of the City of New York, and CARL P. SHERWIN, M.D., SC.D., DR.P.H., LL.D., Member of the Staff of St. Vincent's and French Hospitals, New York. Pp. 797; 52 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, $6.00.

Economic Problems of Medicine. By A. C. CHRISTIE, M.S., M.D., Professor of Clinical Radiology, Georgetown University Medical School, etc. Pp. 242. New York: The Macmillan Company, 1935. Price, $2.00.

Atlas Fundus Oculi. By WILLIAM HOLLAND WILMER, M.D., LL.D.,, Sc.D., Professor of Ophthalmology and Director of the Department of Ophthalmology of the Johns Hopkins University School of Medicine, Ophthalmologist-in-Chief to the Johns Hopkins Hospital, etc. Introduction by WARFIELD T.LONGCOPE, M.D., Professor of Medicine and Director of the Department of Medicine of the Johns Hopkins School of Medicine. Pp. 100; 100 colored plates. New York: The Macmillan Company, 1934. Price, $35.00. (Review, p. 862.)

The Harvey Lectures, Series 29. Delivered under the auspices of The Harvey Society of New York, 1933–1934. Under the patronage of the New York Academy of Medicine. By DRS. R. E. DYER, W. M. CLARK, R. G. HARRISON, E. A. DOISY, E. A. GRAHAM, G. L. STREETER, T. M. RIVERS and D. W. BRONK. Pp. 262; illustrated. Baltimore: The Williams & Wilkins Company, 1935. Price, $4.00.

Failure of the Circulation. By TINSLEY RANDOLPH HARRISON, M.D.- Associate Professor of Medicine, Vanderbilt University School of Medi, cine, Nashville, Tenn. Pp. 396; 60 illustrations and 22 tables. Baltimore: The Williams & Wilkins Company, 1935. Price, $4.50.

Deutsche Volksmedizin. Wissenschaftliche Heilkunde und Kultur. By PAUL DIEPGEN, O. PROF. DR. MED. ET PHIL., BERLIN Pp. 136; 7 illustrations. Stuttgart: Ferdinand Enke, 1935. Price, Geh. Rm. 6.–; Leinen geb., Rm. 7.40.

The Kidney in Health and Disease. Edited by HILDING BERGLUND, M.D., Stockholm, Sweden, formerly Chief of the Department of Medicine at the University of Minnesota, and GRACE MEDES, PH.D., Research Biochemist in the Lankenau Hospital Research Institute, Philadelphia. With the collaboration of G. CARL HUBER, M.D., Professor of Anatomy and Director of Anatomical Laboratories and Dean of the Graduate School of the University of Michigan, WARFIELD T. LONGCOPE, M.D., Professor of Medicine in the Johns Hopkins University, Baltimore, and ALFRED N. RICHARDS, PH.D., M.D., Professor of Pharmacology in the University of Pennsylvania, Philadelphia. Pp. 754; 163 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $10.00.

NEW EDITIONS.

Diseases of the Heart. By JOHN COWAN, B.A., M.D., D.Sc., F.R.F.P.S., sometime Professor of Medicine, Anderson College of Medicine, and Consulting Physician, Royal Infirmary, Glasgow, and W. T. RITCHIE, O.B.E., M.D., F.R.C.P.E., F.R.S.E., Professor of Medicine and of Clinical Medicine, Edinburgh University, and Physician to the Royal Infirmary and Director of the Medical Unit of the Municipal Hospitals, Edinburgh. With a chapter on The Ocular Manifestations of Arterial Disease by ARTHUR J. BALLANTYNE, M.D., F.R.F.P.S., Lecturer on Ophthalmology, University of Glasgow, and Surgeon, Eye Infirmary, etc. Pp. 631; 335 illustrations, some in colors. Third edition. Baltimore: William Wood & Co., 1935. Price, $9.00.

Almost entirely rewritten to keep up with the many recent advances, this book presents tersely the individual views of two foremost authorities in a country that has been a leading contributor to the subject. The authors do not accept the newer terminology for extrasystoles and bundle-branch block.

Recent Advances in Endocrinology. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba, and Biochemist, Winnipeg General Hospital. Pp. 406; 55 illustrations, including 2 plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $5.00.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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DEPRESSIVE REACTIONS IN GENERAL PRACTICE.

NEXT to the psychoneuroses there is probably no other mental disorder met so frequently in the general practice of medicine as the depressive reactions, described by Meyer[1] as "biologically widespread reactions of great individual and social importance, recognizable largely as preoccupations and fixations of the pure affects of sadness and anxiety dependent upon various experiences as bereavement and losses with active or passive suffering." Comprised in this group is that large number of individuals who come to the physician with somatic complaints of one kind or another—head sensations, stomach upsets, pains, aches, constipation, tired feeling, poor sleep and appetite. The physical examination shows appreciably little to account for the sweeping nature of the complaint while diet, teeth extractions, rest cures, and fishing trips fail to solve the problem.

At this point the conscientiously curious physician will investigate further and will learn that the illness had a definite beginning, was precipitated by clear cut situational factors usually in line with personal disappointments or losses to which the patient had responded with worry, anxiety, and concern. The physician will be informed that blueness and sadness best characterize the patient's feelings; that, because of inappetence, he has lost weight, that he is constipated, and that his sex drive is less keen. He may add that generally his spirits improve as the day wears on, though in the morning "life seems unbearable" and that his concentration and memory are "shot." The frequency with which such a patient finds his way to the general practitioner is demonstrated by the report of liaison psychiatry at the Colorado General Hospital[2] where, of 245 cases seen in the 7 months' period, 16.3% were depressions or showed depressive features of primary importance.

Definitely differentiating depressive reactions from the psychoneuroses, or part reactions, is their sweeping character, their biological components—sleep disturbance, loss of weight, constipation, poor

appetite, decreased libido—that point to more serious and widespread involvement of the personality. It is these factors of a biologic nature, associated with suicidal preoccupation so commonly a part of the depressive reactions which call for the most careful consideration by the physician who encounters them.

Though opposed to the tendency of nosological pigeon-holeing, we favor Harrowes'[3] classification of the depressive reactions for the merit it holds in the direction of evaluating etiology and prognosis. He points out six depressive patterns, namely: (*a*) reactive, (*b*) autogenous, (*c*) recurrent, (*d*) psychoneurotic, (*e*) depression with aversion features, and (*f*) involutional types.

In the reactive group, cases are precipitated by difficulties in the life situation. Symptoms beside the formal depression are lack of concentration, loss of interest, insomnia, loss of thought capacity, heightened sense of effort, forgetfulness and headaches. Self-accusation and suicidal preoccupations are not prominent. Etiologic factors are catastrophic or accumulative. With the latter, the illness is more protracted. Of the personality features, there is unimaginativeness and rigidity. Retardation is not marked and insight is variable.

In the group of autogenous depressions, there is no reactivity beyond the initial precipitation. Feelings of remorse and guilt are more marked there is more distortion, retardation, and rut formation, and the affect is not influenced by general factors in the environment or in therapeutic attempts. Suicidal preoccupations are frequent.

The recurrent depressions reveal a history of previous attacks of severity increasing with age. Here, the personality make-up is more definitely depressive in character and agitation and hypochondriasis tends to be more prominent. They are differentiated from recurrent reactive depressions by their more insidious onset and agitation.

Psychoneurotic depressions are chiefly characterized by a prodromal picture of a psychoneurosis, run along course, and are found difficult to modify.

The depressions with aversion, as the term signifies, demonstrate peevishness, occasional paranoid trends in which the patients blame the environment as a handicapping agent, are antagonistic to any therapeutic approach, possess a definite restriction of utilizable interests and inadequate emotional response.

Harrowes' final group, the involutional types, tend to much greater rut formation, entertain schizophrenic-like hypochondriacal delusions, express nihilistic ideas, occur often in presenile women, and are not infrequently terminated by impulsive suicidal acts.

Psychiatric writers have long pointed out the frequency of hereditary taint in the background of individuals suffering from manic-depressive disorders. It has been left, however, to a certain group of writers to investigate this point from a point of view of genetic laws and order. Pollock, Malzberg and Fuller,[4] in an article concerned with the hereditary features involved in manic-depressive psychoses, pointed out their belief that the frequency of mental disease among siblings of the patients with manic-depressive psychoses is consistent with a mode of inheritance based upon the supposed existence of Mendelian unit characters. These works showed conclusively, by careful case studies, that the frequency of mental disorders among the siblings, especially

of manic-depressive psychoses, is significantly in excess of the total expected, in populations selected at random. This was especially true in connection with the siblings of female probands with manic-depressive psychoses. They conclude that there is a familial basis for the development of mental disorders in many cases though the underlying laws of their manner of transmission are not yet understood.

Calling to the attention of the practitioner a particular type of depression frequently masked by the predominance of somatic complaints, is Muncie's article, "Depression with Tension."[5] This group of patients are seen with complaints frequently expressed as the following: "My nerves feel like rubber bands—all a-quiver," "The skin feels stretched over my forehead," "It seems as though there are bubbles and needles in my muscles," "I have the sensations of worms crawling over my skin." Or again, the complaints may be of shooting pains, numbness, trembling, burning, weakness, and quivering in the stomach. In addition to these more obvious physical complaints there are those common to all depressed patients—insomnia, anorexia, and loss of weight. Despite the rather subordinate statements of mood given by these patients, they are invariably observed as sad, brooding, or disinterested, and it is a subordination of mood to the somatic complaints which frequently leads to a wrong diagnosis. Careful investigation procedure revealed the fact that this illness is strongly reactive. In the author's survey of cases, he found that about one-half the group were reactive to sexual difficulties, the others reactive to work dissatisfaction—perhaps promotion, demotion, or the feelings that the responsibilities enforced upon the individual exceeded his capacity to handle them. In this group of depressions, the author found that the situations which lay at the bottom of the problem were still open issues and held possible disaster for the future. In this respect the tension depression differs from the retarded depression in that, in the latter, the patient shows his concern over past events and closed issues. The physiologic expression of tension in these cases is demonstrated by tachycardia, labile pulse, abnormal curve of dextrose tolerance, abnormal findings of gastric secretion, either hypo- or hyper-chlorhydria, exophthalmos, tremors, sweating, flushing, diarrhea, seminal emissions, or an increased sex desire. The evidences of depression are expressed in the mood which is characterized by the patient as "melancholy," "blue," "blessing if I were to die," "I have given up fighting," "I feel a moral weakling," and, objectively, in the appearance of the individual an obvious morning evening variation of mood. The physiologic evidences are again present but perhaps less classical than in other types of depressions. The appetite is usually good, the weight may vary, and there is constipation in about two-thirds of the cases. The sleep demonstrates all manner of variation, though early morning waking is found more frequently than any other type, and irregularities of the sex rhythm may be manifest.

The usual personality background of the tension depression is that of one who is superficially well adjusted, who is accustomed to getting his own way, who is rigid, tenacious, aggressive, and dependent upon his environment. These people usually take responsibilities very seriously, and, as a rule, are very successful in their undertakings. Hypochondriacal trends usually are not a part of the prepsychotic make-up.

Emancipation problems loom prominently in these individuals. The treatment outlined by the author consists essentially of prolonged hospitalization and the obligation of the family to assume all responsibility for the suicidal risk should the patient leave the hospital prematurely. He found that loose, cold, wet packs decreased tension and induced sleep and that, further, the tension could be minimized by small broken doses of barbital, 2½ grains, q.i.d. Belladonna and alkalis were administered in vagotonic gastric intestinal symptoms. He pointed out that the most reliable indications of progress were to be found in paying close attention to the sleep chart, weight graph, and behavior manifestations. Needless to say, a careful, thorough, critical appraisal of the personality was undertaken when the patient was capable of carrying on such an analysis.

Michael[6] defines affect as an awareness of the changes in the body from the impact of environment, or the product of changes in biologic equilibrium from within. The therapeutic approach in affective disorders must follow along lines of causation, somatogenesis, and psychogenesis. Psychotherapy is not limited to psychologic technique but includes all those methods that may be employed in the management of an individual case. Attempts should be made, first, to determine the patient's inherent endowments and constitutional make-up. The therapist must have a reasonable impression of the family setting, the emotional and intellectual development and the social and economic situations. Investigation of the bodily systems is an important consideration. After the therapist has insight into the situations that may be present, or of the disturbing experiences of earlier life that lie at the basis of the patient's reaction, he will decide on the particular method of psychotherapy. He first gives attention to the organic factors and then considers the following: persuasion, suggestion, psychologic reëducation, or personality analysis. The last three methods are most desirable.

The social consideration of this important clinical problem is well brought out in a study of 100 cases of suicide made by Fairbank[7] at Hopkins. Of the 100 cases selected for the survey, 47 were women and 53 men. Seventy-three of them presented "outspoken depression," and 17 of the 24 paranoid and schizophrenic cases showed at least "depressive waves." In the experience of the writer, the motivating factor seemed to be a desire to escape from the mental suffering, from fears or trying environmental situations and disappointments. In more than one-half the cases, the words "hopelessness" and "despair" were encountered. Also, a frequent occurrence was the conviction by the patient that he was "losing his mind" or "going crazy." Spite appeared to be the motive in a few cases while escape from delusional persecution was also found. Two of the group committed suicide to avoid actual situations they could not face.

The writer pointed out as warning signals of suicide the following utterances of patients: "I am an empty shell," "I am guilty," "I am going crazy," "There is no hope for me," and "It is no use going on." The personality characteristics commonly encountered in this group were rigidity, stubbornness, and lack of plasticity. As other writers have shown in the history, depression or other instability was frequently found in collaterals. The methods utilized in suicidal attempts, inter-

estingly enough, were often determined by the prevailing social custom or "style" as indicated in the frequent newspaper reports. The only clinical correlation to be drawn was that perhaps suicide in the schizophrenic was of a more bizarre nature. That there is, as a rule in most cases, warning, this author feels quite sure. Her survey revealed the facts that one-third of the cases gave a very definite indication of danger by having made a previous attempt at suicide and an additional one-third suggested their intention by taking about it. There were 14 cases which gave no intent in this direction or indication other than their tension and restlessness associated with the depression.

In the handling of the potentially suicidal individual a great many problems arise. Premature discharge from the hospital, placing on suicidal observation, guarding against environmental devices which invite the act—all are considerations of importance. Dr. Fairbank points out these warnings and problems and urges prevention by regulations governing the sale of destructive agents because "physicians, the nurses, and the friends of the 'suicide' have reason to feel that with better knowledge and greater care and attention, it might have been possible to prevent what is usually a serious trauma to the unsuccessful and a deplorable event to everybody."

FRANKLIN G. EBAUGH, M.D.

BIBLIOGRAPHY.

1. Meyer, A.: Outline of Pathergasias. (Unpublished.)
2. Semiannual Report of Psychiatric Liaison Activities at Colorado General Hospital, 1934–1935.
3. Harrowes, W. McC.: Depressive Reaction Types, J. Ment. Sci., **79**, 235, 1933.
4. Pollock, H. M., Malzberg, B., and Fuller, R. G.: Hereditary and Environmental Factors in the Causation of Dementia Præcox and Manic-depressive Psychosis, Psych. Quart., **8**, 77, 1934.
5. Muncie, W.: Depressions with Tension; Their Relation to General Problem of Tension, Arch. Neurol. and Psych., **32**, 328, 1934.
6. Michael, J. C.: Treatment of Affective Disorders, Minnesota Med., **16**, 81, 1933.
7. Fairbank, R.: Suicide, J. Am. Med. Assn., **98**, 1711, 1932.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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RELATIONS WITH ADJACENT STRUCTURES.

THERE is a far greater tendency to think of infection spreading to the meninges and brain through some loss of continuity of the bone, such as a congenital dehiscence, a fracture, or some operative trauma than by the blood stream. Therefore, such contiguous pneumatic spaces as the frontal and sphenoid sinuses, the middle ear and mastoid are often accused when in reality the original focus is somewhere more

remote. On our neurosurgical service we have recently had a brain abscess following a peritonsillar abscess and another following a maxillary sinus infection without an osteomyelitis. It is, therefore, very timely that Julius Berendes[1] reports a frontal lobe abscess following an abscess of the septum. This was proven by autopsy. He rightfully states that much has been written about front lobe abscess as a complication of sinus disease, but that in the German literature of the past 12 years no such case as this has been reported. There has been much written about meningitis as a frequent complication of a septal abscess, but none of brain abscess. His case was in a boy, aged 14 years. The abscess was drained. However, on the 19th day the boy developed meningeal signs and unconsciousness. The frontal sinuses were opened and found to be clear. Further operation was refused. Postmortem examination revealed a left frontal lobe abscess, and it was believed that the infection entered the brain by the anterior and posterior ethmoid vessels.

The practice of medicine includes dentistry, and dentistry is a special branch of medicine. To secure efficient coöperation between the two, the dentist should first have a reasonable medical background, and secondly the physician should know sufficient dentistry to understand dental points of view and values. The dentist must recognize the fact that any departure from the normal in the mouth may be the cause, the effect or the symptom of organic disease in other parts of the body. For example, pallor of the skin or mucous membrane should suggest an anemia; edema of the eyelids, a nephritis; enlargement of the thyroid or exophthalmos suggest thyroid investigation; diseased tonsils and adenoids may require attention; an acetone breath should suggest diabetes. Oral syphilis, neoplasms and leukoplakia are frequently seen. The physician should detect the presence of caries, periodontoclasia, malocclusion, poor dental hygiene, fistulas and Vincent's infection. The coöperation of the dentist and the obstetrician in the care of the teeth in the expectant mother is most important. The pediatrician should also know of the harmful habits of thumb sucking, tongue biting, lip interposition and mouth breathing, and of their effect on distorting perfect arches.

The prevention of disease is the cheapest and yet the best service that we can give the public, and for that reason should occupy the most important place in dental and medical education and practice. Next to prevention, the early recognition of disease is the greatest necessity and of the highest service to the public.[2]

A cholesteatoma has been defined by Kopetsky[3] as a globular growth surrounded by a thin shell of epidermis and connective tissue, called the matrix, and composed of accumulated, stratified, horny, desquamated epithelium, devoid of nuclei. Between its lamellæ are found cholesterin crystals in a greater or lesser quantity.

Wittmack[4] explains the formation of cholesteatoma as an attempt by Nature at repair by the growth of the squamous epithelium of the external auditory canal into the middle ear to replace the degenerating mucous membrane. In 1879, Mikulicz,[3] a pathologist, was the first to suggest that cholesteatomatous tumors could arise from an embryonal rest of epidermis. The occurrence of a cholesteatoma in the temporal bone became comprehensible under this theory, since the pinching off

of an epidermal "anlage" in the embryonal sutures is a possible occurrence during the development of the middle ear.

Today we recognize both primary and secondary types of cholesteatomata of the temporal bone, arising from a transplantation of foreign tissues and their growth, the primary being congenital, and the secondary being "postfetal." Anatomically they present the same picture. A secondary cholesteatoma may be identified when there has been a history of earlier or present middle-ear disease.

Day[5] has stated that whether the cholesteatoma is primary, arising from an invagination, pouching and rupturing of Schrapnell's membrane following the formation of adhesions, walling off the attic, or from the middle ear in an infantile otitis of the catarrhal type, or is secondary to a suppurative otitis with an ingrowth of the epidermis of the external canal through a marginal perforation into the middle ear and attic, its development is the same, though the suppuration is a result of the former and the cause of the latter.

The cases diagnosed as primary cholesteatoma of the temporal bone after critical observation are rare and seem to show a predilection to develop in the region of the junction of the temporal, parietal and occipital bones. Recently Beck[6] has reported such a case and has added some interesting remarks about the "art und weise" of the operation performed.

The patient was a girl, aged 20 years, who had had some right-sided deafness for 6 months. Then the development of a facial paralysis sent her to a doctor. At this time the right ear drum looked normal, but there was some deafness. Upon her first examination the vestibular responses were present, but 4 years later upon examination they had disappeared. At this time the patient tended to lean to the right on walking. Roentgen ray showed a large pneumatic mastoid. A Roentgen ray of the petrous tips by Stenver's technique showed a tumor mass, 2 cm. by 1 cm., just under the upper border of the pyramid.

At operation the dura of the middle fossa was widely exposed through the tegmen approach, and by carefully lifting up the dura a cholesteatomatous mass removed, along with as much "matrix" as possible. The patient had a slightly stormy convalescence at first, a positive Kernig and Babinski and a cloudy spinal fluid. In 3 weeks she was out of bed and was discharged at the end of 5 weeks. Electrical treatments were given to the face and the facial weakness was not noticeable after 3 months' time. The deafness and caloric reactions remained unchanged. The author stated that should there be a recurrence from leaving behind some of the matrix he would sacrifice the labyrinth to avoid a recurrence of the facial paralysis. Calcination of the matrix has been observed and Linck has written of findings giving expression to former reports of cell degeneration in the epithelium of the matrix.

In an analysis of 230 patients with carcinoma of the tonsil by Schall,[7] its frequency was found to be 1 in every 106 cancer patients. There appears to be no evidence of increase since 1918. The patient's nationality and occupation did not seem to be factors. The male sex contributed 88.7% of the cases. The age group is that of past middle life. The greatest incidence is found in the group between 60 and 65 years. Only 18 patients gave a family history of carcinoma. There were 42 patients who were non-users of tobacco. In only 48 cases was the

disease limited to the tonsil. In 104 patients the first symptom was pain. The majority of these patients endured their symptoms from 3 to 6 months before consulting a physician. Glandular enlargement occurs fairly early. Cancer of the tonsil was first treated surgically, later by electrosurgery, diathermy or electrocoagulation, and now by the combined use of radium and high-voltage Roentgen ray therapy. In 118 cases in which this treatment was given, 43 cases had no relief, 47 recurred under 1 year; 2 in 1 to 2 years; 2 in 2 to 5 years; and 1 case recurred after 5 years. Of the 23 cases who had no recurrence (18.4%), 5 had died a non-cancerous death.

A new surgical approach to the base of the tongue and lower pole of the tonsil for neoplasm has recently been devised by Dr. D. Macpherson and his associate, Dr. A. Newlands. The operation is done in two stages, the first stage being a tying off of the external carotid artery. A cutting diathermy current is used and completely controls bleeding. Several modifications of this operation are also described.

The Shintz and Coutard schools in Europe do not entirely accept the Broder classification of malignancies. They are endeavoring to identify neoplasms in more detail as to their radiosensitivity and radioresistance. Berven, of Stockholm, reports good results with the use of a 3-gram radium pack. However, the results published by Schall compare favorably with those of Berven and Coutard. Clinically, the results of treatment are encouraging even though a "cure" may not always be obtained.

W. V. MULLIN AND
W. L. DEETON.

REFERENCES.

1. Berendes, J.: Frontal Lobe Abscess Following a Septum Abscess, Ztschr. f. Hals-, Nasen- u. Ohren., **37**, 148, 1934.
2. McLean, R. G.: Coöperation of Physician and Dentist in Prevention and Early Recognition of Disease, J. Am. Dent. Assn., **22**, 72, 1935.
3. Kopetsky, S. J.: Cholesteatoma, Laryngoscope, **43**, 118, 1933.
4. Wittmach, K.: In Henke and Lubarsch's Handb. d. speziel. path. Anat. u. Histol., Berlin, Julius Springer, **12**, 246, 1926.
5. Day, K. M.: Etiologic Factors in Formation of Cholesteatoma, Ann. Otol., Rhinol. and Laryngol., **43**, 837, 1934.
6. Beck, K.: An Operative Case of Primary Cholesteatoma of the Petrous Portion of the Temporal Bone, Ztschr. f. Hals-, Nasen- u. Ohren., **37**, 117, 1934.
7. Schall, LeR. A.: Carcinoma of the Tonsil, Ann. Otol., Rhinol. and Laryngol., **43**, 1047, 1934.

PHYSIOLOGY

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The Plexus Omentalis and Its Relation to Capillary Innervation in the Omentum of Rabbits, With Special Reference to the Unmyogenic Character of Rouget Cells. NICHOLAS A. MICHELS (Daniel Baugh Institute of Anatomy, Jefferson Medical College). By projecting the capillary bed from whole mount preparations of the omentum of

rabbits, then drawing capillary nerves in 325 contiguous oil-immersion fields, a new anatomic support has been found for the physiologic concept of capillary innervation. A nerve plexus was revealed (plexus omentalis) the meshes of which are considerably wider than those of the capillary plexus itself. It consists of numerous non-medullated nerve fibers which pertain to the category of plasmodial nerve strands (Remak fibers), now regarded as the ultimate terminations of the autonomic system. The 1-micron wide Schwannian nucleated capillary nerves run parallel, cross over, under, accompany, and often become lost in the capillary wall. Since many capillaries have no nerves, and since terminal knob-like endings on endothelium were never found (no one has ever seen them with certainty on capillaries), it is concluded that capillary innervation is effected as a physiologic unit, the nervous syncytium functioning at contact points with self-contracting endothelium. In fixed and vitally stained preparations there was no evidence of the muscular character or innervation of Rouget cells. Pericapillary oblong cells prevailingly represent pericytes; a goodly quota have been mistaken for nucleated segments of capillary Remak fibers. A study of living capillaries in the web of the frog under normal and experimental conditions confirmed the contractile power of endothelium and the non-myogenic character of Rouget cells.

Effect of Dorsal Root Stimulation on the Properties of the Muscles of Bloodvessels. EMIL BOZLER (Johnson Foundation, University of Pennsylvania). A study was made of the changes in the properties of smooth muscle under the influence of stimulation of inhibitory nerves. A frog hindleg was perfused. The contractions of the muscles of the arterial system were measured by recording the flow, using a sensitive flowmeter. It was found that dorsal root stimulation suppresses the effect of sympathetic stimulation completely if the stimuli follow one another at long intervals. If they are applied at a high frequency the response is not appreciably influenced by simultaneous dorsal root stimulation. The results can be quantitatively interpreted on the basis of the chemical intermediators. The inhibition seems to be due to an immediate antagonism of the two intermediators produced by stimulation of the sympathetic and the vasodilators without any effect on the contractile mechanism as such. It is, furthermore, found that dorsal root stimulation greatly accelerates the relaxation. From stretching experiments it is concluded that the rate of relaxation is essentially determined by the viscous properties. The experiments give evidence that dorsal root stimulation decreases the viscosity of the muscles of the arteries.

The Absorption of Glucose and Galactose From the Dog's Intestine. F. A. CAJORI and WALTER G. KARR (Laboratory of Physiological Chemistry, University of Pennsylvania). The rates of absorption of glucose and galactose from Thiry loops of the jejunum of dogs have been studied. When solutions containing both these sugars were inserted into the loop, glucose was absorbed more rapidly than galactose, the total carbohydrate absorption being about the same as when the sugars were given separately. However, no difference was found

in the rate of absorption of glucose and galactose when administered separately.

There was no indication that in the presence of phosphates the rate of glucose, galactose or fructose absorption was increased. These results, which are contrary to those reported by Magee and Reid,[1] are of interest when considering the hypothesis that the mechanism of sugar absorption involves phosphorus compounds. The rate of sugar absorption was not changed in the presence of sulphate or chlorid.

One-half to one hour following the administration of isotonic solutions, the osmolar concentration of the loop contents remained close to the accepted value for dog's blood. Water was not absorbed as rapidly as sugar, the absorbed sugar being replaced by chlorid. When the solutions introduced into the intestinal loop had an osmotic pressure twice that of the blood, an hour's time was hardly sufficient for the attainment of osmotic equilibrium. Analysis showed, however, that chlorid had entered the hypertonic solution.

Glycogen was isolated from dog's liver after a period of galactose feeding and compared with dog's liver glycogen isolated after glucose feeding. The two glycogens were hydrolyzed at the same rate with H_2SO_4, salivary amylase and taka-diastase. They exhibited the same specific rotation before and after hydrolysis. It was concluded that they were identical chemically.

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1. A Study of the Gall-bladder Bile in Pregnancy at Term. 2. A Study of the Gall-bladder Bile in Calculous and Non-calculous Cholecystitis. 3. A Study of White Bile. C. RIEGEL, I. S. RAVDIN, C. G. JOHNSTON and P. J. MORRISON (Laboratory of Research Surgery, University of Pennsylvania). Data on the composition of bile from the human gall bladder in the following conditions were given: (1) In pregnancy at term; (2) in non-calculous and calculous cholecystitis; and (3) in hydrops.

The mean calcium concentrations in all five groups were below normal, the average values being for the pregnancy group (A) 15 m Eq./L.;[2] for the non-calculous cholecystitis group (B), 16 m Eq./L.; for the calculous cholecystitis group in which the gall bladder was visualized after sodium tetraiodophenolphthalein (C), 15 m Eq./L.; for the calculous group in which the gall bladder was not visualized after dye administration (D), 10 m Eq./L.; and in the hydrops group (E), 10 m Eb./L.

The mean chlorid concentrations were above normal in all five groups and the concentration increased with increasing disturbances of biliary tract function. The average values were for (A) 46, for (B) 57, for (C) 61, for (D) 102 and for (E) 113 m Eq./L.

The mean bile salt concentrations were lower than normal in all five groups. The highest values were found in the pregnancy and non-calculous groups, while in hydrops bile salts were absent. Mean values were for (A) 2653, for (B) 2813, for (C) 1560, for (D) 607 and for (E) 0 mg. per 100 cc.

The mean cholesterol concentrations were higher than normal in the first three groups: (A) 376 mg., (B) 383 and (C) 487 mg. per 100 cc.; in (D) cholesterol dropped to 133 and in (E) to 14 mg. per 100 cc.

[1] Magee, H. E., and Reid, E.: J. Physiol., **73**, 163, 1932.

[2] m Eq./L. = milliequivalents per liter.

These five groups illustrate progressive stages in the development of a damaged gall bladder and the production of gall stones, the pregnancy and non-calculous groups being the most nearly normal, while the "white bile" group shows the greatest variation from the normal. The condition of lowered calcium and increased chlorid concentration is indicative of damage to the gall-bladder wall. The high cholesterol values in groups (A) and (B) probably indicate that a bile abnormally high in cholesterol is being excreted into the gall bladder from the liver, since there were no indications at operation of an inflammatory lesion of the gall-bladder. The low bile salt concentration may be due to a reduced amount of bile salt in the hepatic bile or to a more rapid absorption of bile salt in the gall bladder. It would appear from the summary of data given here that an increase in cholesterol concentration or a decrease in bile salt, or both, may be the initial factor in stone formation. That these factors alone are not sufficient, however, is evident from the absence of stones in the cases of the non-calculous and pregnancy groups, although in many instances in these two groups there was evidence of both an abnormal hepatic bile and a damaged gall-bladder wall.

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INDEX.

(The page numbers of original articles appear in black face type. Original articles are indexed under each author's name, and under one or more subject heads of the title; abstracted articles are less fully cross-indexed; all book reviews are indexed singly under the head of "Reviews," according to the author's name.)

A

Acacia, hypoproteinemic nephrosis and treatment with; 2 "cured" cases, **536**
Acetyl-β-methylcholin (mecholin); its action, blood pressure, etc., **55**
Addison's disease, suprarenal extract and sodium salts' use in, **419**
Adrenalectomized-depancreatized and hypophysectomized - depancreatized cats, 597
Adrenals of tumor-bearing rats, histologic changes in, **423**
Agranulocytosis, bone marrow in, **507**
Albino rat, prolonged exercise effects, on weights of organs of, 155
"Alcoholic" polyneuritis, etiology of, **378**
Anemia, macrocytic, and hepatic cirrhosis, **115**
with aplastic features after synthetic organic hair dye, **759**
Anesthetics, volatile, oxygen effect in prevention of liver necrosis produced by, 155
Angina pectoris and heart failure, treatment of, by total thyroidectomy, 727
observations on prognosis in, **690**
Antidiuretic and pressor substances, failure to find, in toxemia of pregnancy patients, **613**
Appendicitis, acute, 290
and acute salpingitis, sedimentation time as differentiation aid in, **383**
Arachnidism, effective treatment of, by calcium salts, **532**
Arnold, H. L., Middleton, W. S., and Chen, K.K., action of thevetin, a cardiac glucosid and clinical application, **193**
Arsphenamins, intravenous, myelitis and so-called hemorrhagic encephalitis, secondary to; 158 cases, **64**
Arteriovenous fistula effect on human circulation, 154, **497**
Asbestosis, pulmonary, sputum study in, **44**
Auricular fibrillation in hyperthyroidism; age influence, **683**
Autopsies, obtaining permissions for, **341**

B

Bacteria, effect on normal stomach and acute experimental gastric ulcer in dogs, **696**
Bacteriophage, clinical application of polyvalent staphylococcus, in bronchoscopy, **91**
Baldridge, C. W., macrocytic anemia with aplastic features after synthetic organic hair dye, **759**
Bamber, J. M., electrocardiographic changes after potassium iodid in syphilitic heart disease, **681**
Barach, J. H., and Boyd, D. M., hypoproteinemic nephrosis and treatment with acacia; 2 "cured" cases, **536**
Barker, N. W., Brown, G. E., and Roth, G. M., tissue extracts' effect on muscle pains of ischemic origin (intermittent claudication), **36**
Bayer, L. M., and Gray, H., obesity treatment by diet, thyroid and dinitrophenol; 106 outpatients, **86**
Bence-Jones proteinemia in multiple myeloma, **425**
Bethea, J. M., and Foot, N. C., *see* Reznikoff, P., **753**
Bichlorid of mercury acute poisoning, renal injury in, with treatment note, **392**
Bichromate, acute potassium, poisoning, **400**
Bierman, W., and Derow, D., *see* Horowitz, E. A., **555**
Bile, white, 881
Blankenhorn, M. A., and Hayman, J. M., Jr., suprarenal extract and sodium salts' use in Addison's disease, **419**
Block, F. B., ovarian tumors, 581
Blood, clinical estimation and significance of calcium-ion concentrations in, **601**
glucose clearance; microinterval method determination. I. Normal and diabetic persons, **702**
pressure, variations in, in renal tuberculosis, **803**
sedimentation test, standardized technique for, **102**
transfusion, factors conditioning transmission of syphilis by, **808**
vessel endothelium, changes in, 599
vessels, muscles of, dorsal root stimulation on, 880

Blood, whole, phagocytic power of, or plasma-leukocyte mixtures for clinical and experimental purposes; improved method, **27**
Blumenthal, R. W., and Oesterlin,, E. J., spindle cell sarcoma of pancreas, **784**
Boerner, F., and Mudd, S., phagocytic power of whole blood or plasma-leukocyte mixtures for clinical or experimental purposes; improved method, **22**
Bohning, A., and Katz, L. N., four-lead electrocardiogram in coronary sclerosis; consecutive patients' series, **833**
Bone marrow, different cell counts of; infrequently appearing cell types, **630**
structure and function of. IV. Bone marrow in agranulocytosis, **507**
Boyd, D. M., *see* Barach, J. H., **536**
Brain, is there a "moral center" in the, **265**
Brams, W. A., and Golden, J. S., early response to venesection on so-called bloodless venesection, **813**
Bronchoscopy, clinical application of polyvalent staphylococcus bacteriophage in, **91**
Brown, G. E., and Roth, G. M., *see* Barker, N. W., **36**
see Goldsmith, G. A., **819**
L., and Sampson, H. L., pulmonary tuberculosis treatment, **325**
Bullock, L. T., *see* Hurwitz, D., **613**

C

Calcium salts, effective treatment of arachnidism by, **532**
Calcium-ion concentrations in blood, clinical estimation and significance of, **601**
Cannon, W. B., stresses and strains of homeostasis, **1**
Cantarow, A., Bence-Jones proteinemia in multiple myeloma, **425**
Capillary innervation in rabbits' omentum, plexus omentalis relationship to, 879
Cardiac rhythm, mechanisms of; unusual human electrocardiograms, **657**
Cardiovascular response to subcutaneous injection of epinephrin and pituitrin in essential hypertension, **215**
Carter, J. B., and Traut, E. F., quinidin and strychnin in treatment of premature contractions, **206**
Cell counts, differential, of bone marrow; infrequently appearing cell types, **630**
Chen, K. K., and Middleton, W. S., *see* Arnold, H. L., **193**
Childbirth and pregnancy, intrapleural pressure in artificial pneumothorax during, **119**
Cholecystitis, calculous and non-calculous, gall bladder bile in, 881
Chorea, treatment of, 145
Circulation, human, arteriovenous fistula effect on, 154, **497**
Cirrhosis, hepatic, and macrocytic anemia, **115**
Cohn, A. E., and Lewis, W. H., Jr., lobar pneumonia and digitalis, **457**
Comroe, B. I., Thomsen's disease (myotonia congenita), **714**
Coronary disease, value in, of standardized exercise effect on four-lead electrocardiogram, **346**
sclerosis, four-lead electrocardiogram in; consecutive patients' series, **833**
thrombosis and its effect on heart size, **858**
serial electrocardiograms in, **487**
Crile, G., pathologic physiology of neuroglandular system, **276**
Crimm, P. D., and Short, D. M., vitamin A content of human liver, **571**
Custer, R. P., and Krumbhaar, E. B., histopathology of hemopoietic tissues in hemophilia; unexplored field, **620**
see Krumbhaar, E. B., **630**
structure and function of bone marrow. IV. Bone marrow in agranulocytosis, **507**
Cystinuria case study; sulphur metabolism, 301
Cysts, congenital, of lung, **788**
Cytoplasmic changes in peripheral neutrophil as diagnosis and prognosis aid, **639**

D

Deeton, W. L., *see* Mullin, W. V., 876
Dentistry, relation of, to medicine, **15**
Derivaux, R. C., and Hewell, B., *see* Robinson, C. S., **795**
Dermatitis gangrenosa; diabetes mellitus complication, **550**
Derow, D., and Bierman, W., *see* Horowitz, E. A., **555**
Dextrose and starch effects on glycemia and glycosuria in diabetics, **545**
(Deuterium oxid) heavy water, living cells permeability to, 456
Diabetes mellitus, changing cause of death in, **157**

Diabetes mellitus, complication; dermatitis gangrenosa, **550**
duodenal extract (Macallum-Laughton) in, **403**
studies in, III, **163**
Diabetics, dextrose and starch effects on glycemia and glycosuria in, **545**
Diaphragmitis, acute primary (Hedblom's syndrome), **566**
Diathermy, temperature determinations in female pelvis during, **555**
Diet, thyroid and dinitrophenol, obesity treatment by; 106 outpatients, **86**
Differential cell counts of bone marrow; infrequently appearing cell types, **630**
Digitalis and lobar pneumonia, **457**
Dilaudid (dihydromorphinone hydrochlorid) and morphin actions on dog intestine, 455
Dinitrophenol, diet and thyroid, obesity treatment by; 106 outpatients, **86**
Dorsal root stimulation on muscles of bloodvessels, 880
Dublin, L. I., and Marks, H. H., *see* Joslin, E. P., **163**
Duncan, G. G., Shumway, N. P., Williams, T. L., and Fetter, F., duodenal extract (Macallum-Laughton) in diabetes mellitus, **403**
Duodenal extract (Macallum-Laughton) in diabetes mellitus, **403**
Dyestuffs' secretion by kidneys, 303

E

Ebaugh, F. G., depressive reactions in general practice, 872
Eggleston, C., treatment of heart failure and angina pectoris by total thyroidectomy, 727
Electrocardiogram, four-lead, in coronary sclerosis; consecutive patients' series, **833**
standardized exercise effect on; value in coronary disease, **346**
Electrocardiograms, serial, in coronary thrombosis, **487**
Electrocardiographic changes after potassium iodid in syphilitic heart disease, **681**
Eller, J. J., and Schonberg, I. L., metastatic melanocarcinoma with apparent recovery, **240**
Elliot, A. H., and Nuzum, F. R., cardiovascular response to subcutaneous injection of epinephrin and pituitrin in essential hypertension, **215**
Embolism, paradoxical, **236**
Encephalitis, epidemic; St. Louis outbreak of 1933, 450
Encephalitis, epidemic; so-called hemorrhagic, and myelitis secondary to intravenous arsphenamins; 158 cases, **64**
Endothelium, bloodvessel, changes in, 599
Eosinophilic leukemia, acute, **387**
Epidemic encephalitis; St. Louis outbreak of 1933, 450
Epinephrin and pituitrin in essential hypertension, cardiovascular response to subcutaneous injection of, **215**
vascular response sensitivity to, after plasma injection from nephritic patients, **371**
Ervin, C. E., and Niles, J. S., *see* Hunt, H. F., **95**
Esophagus, spontaneous rupture of, in syphilis, **80**
Ethylene dichlorid poisoning, fatal, **778**
Exercise, prolonged, effects of, on weights of organs of albino rat, 155
standardized, effect on four-lead electrocardiogram; value in coronary disease, **346**

F

Facial paralysis, recurrence of, **270**
Fat metabolism, recent studies on, 134
Faulkner, J. M., Place, E. H., and Ohler, W. R., scarlet fever effect upon the heart, **352**
Feldman, M., *see* Morrison, S., **696**
Fetter, F., Shumway, N. P., and Williams, T. L., *see* Duncan, G. G., **403**
Freyberg, R. H., and Lashmet, F. H., renal injury in bichlorid of mercury acute poisoning, with treatment note, **392**
Fistula, arteriovenous, effect of, on human circulation, 154, **497**
Flynn, J. M., changing cause of death in diabetes mellitus, **157**
Foot, N. C., and Bethea, J. M., *see* Reznikoff, P., **753**
Four-lead electrocardiogram in coronary sclerosis; consecutive patients' series, **833**
standardized exercise effect on; value in coronary disease, **346**
Freeman, W., *see* Glass, W. E., **80**

G

Galactose and glucose absorption from dog's intestine, 880
Gall bladder bile in pregnancy at term; in calculous and non-calculous cholecystitis; and white bile, 881

Gangrenosa, dermatitis; diabetes mellitus complication, **550**
Garner, V. C., *see* Stokes, J. H., 590
Gastric physiology in man, III, 598
ulcer, acute experimental, and normal stomach in dogs, bacteria effect on, **696**
Gilbert, E. W., and Stewart, C. M., effective treatment of arachnidism by calcium salts, **532**
Glaser, M. A., Imerman, C. P., and Imerman, S. W., so-called hemorrhagic encephalitis and myelitis secondary to intravenous arsphenamins; 158 cases, **64**
Glass, W. E., and Freeman, W., spontaneous rupture of esophagus in syphilis, **80**
Glucose and galactose absorption from dog's intestine, 880
clearance, blood; microinterval method. I. Normal and diabetic persons, **702**
Glycemia and glycosuria in diabetics, dextrose and starch effects on, **545**
Glycosuria and glycemia in diabetics, dextrose and starch effects on, **545**
factors affecting appearance and duration of, **795**
Golden, J. S., *see* Brams, W. A., **813**
Goldman, M., and Karotkin, R. H., acute potassium bichromate poisoning, **400**
Goldsmith, G. A., and Brown, G. E., pain in thrombo-angiitis obliterans; clinical study of 100 consecutive cases, **819**
Goodman, M., mechanisms of cardiac rhythm; unusual human electrocardiograms, **657**
Granulocytopenia, chronic, of 5 years' duration with recurrent acute attacks; case report, **633**
Gray, H., *see* Bayer, L. M., **86**

H

Hair dye, synthetic organic, macrocytic anemia with aplastic features after, **759**
Harper, T., and Watson, A., *see* Smith, C. T., **383**
Hastings, A. B., *see* McLean, F. C., **601**
Hayman, J. M., Jr., *see* Blankenhorn, M. A., **419**
Heart, coronary thrombosis and its effect on size of, **858**
disease, left axis deviation with and without, **674**
Heart disease, syphilitic, electrocardiographic changes after potassium iodid in, **681**
failure and angina pectoris, treatment of, by total thyroidectomy, 727
scarlet fever effect upon the, **352**
Heavy water (deuterium oxid), living cells permeability to, 456
(Hedblom's syndrome) acute primary diaphragmitis, **566**
Hematology, clinical, diagnostic value of sternal puncture in, **515**
Hemoglobin derivatives, analysis of spectra of, 154
Hemophilia, histopathology of hemopoietic tissues in, **620**
Hewell, B., and Derivaux, R. C., *see* Robinson, C. S., **795**
Hirschboeck, F. J., paradoxical embolism, **236**
Histamin and leukocytosis, 455
Histologic changes in adrenals of tumor-bearing rats, **423**
Histopathology of hemopoietic tissues in hemophilia; unexplored field, **620**
Hitzrot, L. H., *see* Landis, E. M., **305**
Holman, W. L., studies on staphylococci, 436
Homeostasis, stresses and strains of, **1**
Horine, E. F., and Weiss, M. M., coronary thrombosis and its effect on heart size, **858**
Horowitz, E. A., Derow, D., and Bierman, W., temperature determinations in female pelvis during diathermy, **555**
Horton, B. T., *see* Morlock, C. G., **803**
Hueper, W. C., and Smith, C., fatal ethylene dichlorid poisoning, **778**
Human circulation, effects of arteriovenous fistula on, 154, **497**
Hunt, H. F., Ervin, C. E., and Niles, J. S., foreign protein therapy, I, **95**
Hurwitz, D., and Bullock, L. T., failure to find pressor and antidiuretic substances in toxemia of pregnancy patients, **613**
Hypertension, essential, cardiovascular response to subcutaneous injection of epinephrin and pituitrin in, **215**
kaolin, studies in mechanism of, 750
malignant, malignant nephrosclerosis, **221**
Hyperthyroidism, auricular fibrillation in; age influence, **683**
Hypophysectomized - depancreatized and adrenalectomized-depancreatized cats, 597
Hypoproteinemic nephrosis and treatment with acacia; 2 "cured" cases, **536**

I

IMERMAN, C. P., and Imerman, S. W., *see* Glaser, M. A., **64**
Intestine of dog, morphin and dilaudid (dihydromorphinone hydrochlorid) actions on, 455
Intrapleural pressure in artificial pneumothorax during pregnancy and childbirth, **119**

J

JOANNIDES, M., acute primary diaphragmitis (Hedblom's syndrome), **566**
Johnson, R. M., pneumonia in undulant fever; 3 case reports, **483**
Johnston, C. G., *see* Ravdin, I. S., 290
Joslin, E. P., Dublin, L. I., and Marks, H. H., studies in diabetes mellitus, III, **163**

K

KANE, A. P., *see* Wishnofsky, M., **545**
Kaolin hypertension, studies in mechanism of, 750
Karotkin, R. H., *see* Goldman, M., **400**
Katz, L. N., and Landt, H., standardized exercise effect on four-lead electrocardiogram; value in coronary disease, **346**
see Bohning, A., **833**
Kidney, dyestuffs' secretion by, 303
Krumbhaar, E. B., and Custer, R. P., differential cell counts of bone marrow; infrequently appearing cell types, **630**
see Custer, R. P., **620**

L

LANDIS, E. M., and Hitzrot, L. H., alternate suction and pressure in advanced peripheral vascular disease treatment, **305**
Landsberg, J. W., *see* Wintrobe, M. M., **102**
Landt, H., *see* Katz, L. N., **346**
Laplace, L. B., arteriovenous fistula effect on human circulation, **497**
Lashmet, F. H., *see* Freyberg, R. H., **392**
Left axis deviation with and without heart disease, **674**
Leukemia, acute eosinophilic, **387**
neurologic aspect of, **766**
Leukocytosis and histamin, 455
Lewis, G. M., ringworm of scalp; curability, etc., **364**
W. H., Jr., *see* Cohn, A. E., **457**
Liebermann-Burchard reaction velocities of sterols, I, II, 302
Liver, human, vitamin A content of, **571**
necrosis produced by volatile anesthetics, oxygen effect in prevention of, 155
therapy, parenteral, in streptococcus pneumonia, **374**
Living cells' permeability to heavy water (deuterium oxid), 456
Lloyd, J. J., and Richard, E. K., intrapleural pressure in artificial pneumothorax during pregnancy and childbirth, **119**
Lobar pneumonia and digitalis, **457**
Love, J. W., *see* Moore, W. F., **91**
Lung, congenital cysts of, **788**

M

MACHT, D. I., ultraviolet rays' effect on snake venoms, **520**
MacMahon, H. E., and Pratt, J. H., malignant nephrosclerosis (malignant hypertension), **221**
Macrocytic anemia with aplastic features after synthetic organic hair dye, **759**
Magee, H. R., and Smith, H. L., auricular fibrillation in hyperthyroidism; age influence, **683**
Marks, H. H., and Dublin, L. I., *see* Joslin, E. P., **163**
McCoy, G. W., epidemic encephalitis; St. Louis outbreak of 1933, 450
McEuen, C. S., and Selye, H., histologic changes in adrenals of tumor-bearing rats, **423**
McKean, R. M., Myers, G. B., and Von der Heide, E. C., blood glucose clearance, microinterval method determination. I. Normal and diabetic persons, **702**
McLean, F. C., and Hastings, A. B., clinical estimation and significance of calcium-ion concentrations in blood, **601**
(Mecholin) acetyl-β-methylcholin; its action in blood pressure, etc., **55**
Medicine, relation of dentistry to, **15**
Melanocarcinoma, metastatic, with apparent recovery, **240**
Mendell, T. H., and Meranze, T., *see* Meranze, D. R., **639**
Meranze, D. R., Mendell, T. H., and Meranze, T., cytoplasmic changes in peripheral neutrophil as diagnosis and prognosis aid, **639**
Merwarth, H. R., recurrence of facial paralysis, **270**
Metabolism, fat, recent studies on, 134
sulphur; cystinuria case study, 301

Middleton, W. S., and Chen, K. K., *see* Arnold, H. L., **193**
Migraine physique, **359**
Mills, C. A., susceptibility to tuberculosis: race or energy level? **330**
Miner, L. M. S., relation of dentistry to medicine, **15**
Minnich, W. R., *see* Proger, S. H., **674**
Moore, W. F., and Love, J. W., clinical application of polyvalent staphylococcus bacteriophage in bronchoscopy, **91**
"Moral center," is there a, in the brain? **265**
Morgan, H. J., factors conditioning transmission of syphilis by blood transfusion, **808**
Morlock, C. G., and Horton, B. T., variations in blood pressure in renal tuberculosis, **803**
Morphin and dilaudid (dihydromorphinone hydrochlorid) actions on dog intestine, 455
sulphate action upon movement of small intestine in man, 751
Morrison, S., and Feldman, M., bacteria effect on normal stomach and acute experimental gastric ulcer in dogs, **696**
Mudd, S., *see* Boerner, F., **22**
Mullin, W. V., and Deeton, W. L., relations with adjacent structures, 876
Muscle pains of ischemic origin (intermittent claudication), tissue extracts' effect on, **36**
Myelitis and so-called hemorrhagic encephalitis, secondary to intravenous arsphenamins; 158 cases, **64**
Myeloma, multiple, Bence-Jones proteinemia in, **425**
Myers, G. B., and Von der Heide, E. C., *see* McKean, R. M., **702**
(Myotonia congenita) Thomsen's disease, **714**

N

Nephritic patients, vascular response sensitivity to epinephrin after plasma injection from, **371**
Nephrosclerosis, malignant (malignant hypertension), **221**
Nephrosis, hypoproteinemic, and treatment with acacia; 2 "cured" cases, **536**
Nerve impulses in single fibers of vertebrate retina, 751
Neuroglandular system, pathologic physiology of, **276**
Neutrophil, cytoplasmic changes in peripheral, as diagnosis and prognosis aid, **639**
Niles, J. S., and Ervin, C. E., *see* Hunt, H. F., **95**
Nuzum, F. R., *see* Elliot, A. H., **215**

O

Obesity treatment by diet, thyroid and dinitrophenol; 106 outpatients, **86**
Oesterlin, E. J., and Blumenthal, R. W., spindle cell sarcoma of pancreas, **784**
Ohler, W. R., and Place, E. H., *see* Faulkner, J. M., **352**
Oto-rhino-laryngology, relations with adjacent structures, 876
Ovarian tumors, 581
Oxygen effect in prevention of liver necrosis produced by volatile anesthetics, 155

P

Page, I. H., acetyl-β-methylcholin (mecholin); its action on blood pressure, etc., **55**
vascular response sensitivity to epinephrin after plasma injection from nephritic patients, **371**
R. C., sputum study in pulmonary asbestosis, **44**
Pagel, W., endogenous origin of early pulmonary tuberculosis; anatomic view of clinical diagnosis, **253**
Pancreas, spindle cell sarcoma of, **784**
Paradoxical embolism, **236**
Paralysis, facial, recurrence of, **270**
Pelvis, female, temperature determinations in, during diathermy, **555**
Peripheral neutrophil, cytoplasmic changes in, as diagnosis and prognosis aid, **639**
vascular disease, advanced, alternate suction and pressure in treatment of, **305**
Permeability of living cells to heavy water (deuterium oxid), 456
Physiology, pathologic, of neuroglandular system, **276**
Pigmentosa, retinitis, 297
Pituitrin and epinephrin in essential hypertension, cardiovascular response to subcutaneous injection of, **215**
Place, E. H., and Ohler, W. R., *see* Faulkner, J. M., **352**
Plasma injection from nephritic patients, vascular response sensitivity to epinephrin after, **371**
-leukocyte or whole blood mixtures, phagocytic power of, for clinical or experimental purposes; improved method, **22**
Plexus omentalis relationship to capillary innervation in rabbits' omentum, 879

Pneumonia in undulant fever, 3 case reports, **483**
lobar, and digitalis, **457**
streptococcus, parenteral liver therapy in, **374**
Pneumothorax, artificial, intrapleural pressure in, during pregnancy and childbirth, **119**
Poisoning, acute potassium bichromate, **400**
bichlorid of mercury acute, renal injury in, with treatment note, **392**
fatal ethylene dichlorid, **778**
Polycythemia vera, etiologic and pathologic factors in, **753**
Polyneuritis, "alcoholic," etiology of, **378**
Potassium bichromate poisoning, acute, **400**
iodid, electrocardiographic changes after, in syphilitic heart disease, **681**
Practice, general, depressive reactions in, 872
Pratt, J. H., *see* MacMahon, H. E., **221**
Pregnancy and childbirth, intrapleural pressure in artificial pneumothorax during, **119**
at term, gall-bladder bile in, 881
patients, toxemia of, failure to find pressure and antidiuretic substances in, **613**
Premature contractions, quinidin and strychnin in treatment of, **206**
Pressor and antidiuretic substances, failure to find, in toxemia of pregnancy patients, **613**
Proger, S. H., and Minnich, W. R., left axis deviation with and without heart disease, **674**
Prognosis, observations on, in angina pectoris, **690**
Proteinemia, Bence-Jones, in multiple myeloma, **425**
Protein therapy, foreign, I, **95**
Pulmonary tuberculosis, endogenous origin of early; anatomic view of clinical diagnosis, **253**
treatment of, **325**

Q

QUINIDIN and strychnin in treatment of premature contractions, **206**

R

RADIOTHERAPY, 742
Ravdin, I. S., and Johnston, C. G., acute appendicitis, 290
Reactions, depressive, in general practice, 872
Reducing materials, excretion of, in urine of normal dog, 454
Reflex thresholds in cat during spinal shock, 303
Reich, C., diagnostic value of sternal puncture in clinical hematology, **515**
Renal injury in bichlorid of mercury acute poisoning, with treatment note, **392**
tuberculosis, variations in blood pressure in, **803**
Retinitis pigmentosa, 297
Reviews:
Abbott, Journal of Technical Methods and Bulletin of the International Association of Medical Museums, No. XIV, 867
Abt, The 1934 Year Book of Pediatrics, 868
Berzelius, Jöns Jacob, 126
Bluemel, Stammering and Allied Disorders, 724
Brailsford, The Radiology of Bones and Joints, 282
Brown, Rules for Recovery from Pulmonary Tuberculosis, 124
Carlisle, Practical Talks on Heart Disease, 283
Clapp, Cataract, Its Etiology and Treatment, 125
Clendening, Methods of Treatment, 867
Cold Spring Harbor Symposia on Quantitative Biology, Vol. 2, 577
Coman, The Technique of Postmortem Examination, 724
Cowgill, The Vitamin B Requirement of Man, 723
Craig, Amebiasis and Amebic Dysentery, 281
Creutz, Die Neurologie des 1.–7. Jahrhunderts N. Chr. Eine historisch-neurologische Studie, 724
Dandy, Benign Encapsulated Tumors in the Lateral Ventricles of the Brain, 431
Davis, Applied Anatomy, 130
The Advance of Science, 574
Davison, The Compleat Pediatrician, 129
DeLee and Greenhill, The 1934 Year Book of Obstetrics and Gynecology, 869
Dimmitt, Manual of Clinical Laboratory Methods, 286
Dodson, Synopsis of Genitourinary Diseases, 286
Duncan, Diabetes Mellitus and Obesity, 861
Fischel, The Spastic Child, 285
Fischer, Gracian's Manual, 287
Fracastoro, Syphilis or the French Disease, 864
Fraser, The Principles of Therapeutics, 721
Gershenfeld, The Jew in Science, 578

Reviews—
Gerson, Diättherapie der Lungentuberkulose, 432
Goldthwait, Brown, Swaim and Kuhns, Body Mechanics, 574
Goodman, Benjamin Rush, Physician and Citizen, 128
Graham, Singer and Ballon, Surgical Diseases of the Chest, 861
Haggard, The Doctor in History, 131
Hammond, The Constitution and Its Reaction in Health, 429
Hardy, To Remind: A Biological Essay, 721
Hatcher and Eggleston, Useful Drugs, 867
Hentschel and Cook, Biology for Medical Students, 574
Hess, Mohr, and Bartelme, The Physical and Mental Growth of Prematurely Born Children, 575
John, Diabetic Manual for Patients, 287
Kapferer and Stricker, Die Werke des Hippokrates, 864
Kessler, The Crippled and the Disabled, 575
Klinik der Erkrankungen des Herzmuskels, X, 868
Koch, Verhandlungen der deutschen Gesellschaft für Kreislaufforschung, 285
Kuntz, The Autonomic Nervous System, 124
Laignel-Lavastine and Molinery, French Medicine, 863
Landon and Smith, Poliomyelitis, 722
Laquer, Hormone und innere Sekretion, 284
Lartschneider, Krebs im Lichte biologischer und vergleichend anatomischer Forschung, 283
[Lea], One Hundred and Fifty Years of Publishing, 1785–1935, 570
Leschke, Clinical Toxicology, 126
Livingston, The Clinical Aspects of Visceral Neurology, 576
Loeb, Martini's Principles and Practice of Physical Diagnosis, 865
Macleod, Physiology in Modern Medicine, 865
Martin, Fifty Years of Medicine and Surgery, 284
Meaker, Human Sterility, 125
Medical Clinics of North America, Vol. 18, No. 3 (New York Number—November, 1934), 577
Meigs, Tumors of the Female Pelvic Organs, 430
Mohr, Heredity and Disease, 429
Morton, Human Anatomy, Double Dissection Method, 576
Musser, Internal Medicine, 124
Ogino, Conception Period of Women, 281
Petersen, The Patient and the Weather, Vol. III, 282
Piersol and Bortz, The Cyclopedia of Medicine, Index to Vols. 1 to 12, 863
Reviews—
Polevski, The Heart Visible, 430
Power, Studies in Blood Formation, 130
Prinz and Greenbaum, Diseases of the Mouth and Their Treatment, 721
Pritchard, The New-born Baby, 722
Rohrer, Researches in Cancer; Part 1 (1896–1921; 1922–1932), 287
Ruggles, Mental Health: Past, Present and Future, 283
Sabin, Franklin Paine Mall, Anatomist, 433
Semon, An Atlas of the Commoner Skin Diseases, 578
Sherman, Food and Health, 722
Sibley, Elementary Human Anatomy, 575
Sigerist, American Medicine, 723
Smith, Parasitism and Disease, 127
Springstun, Doctors and Juries, 868
Spurling, Practical Neurological Diagnosis, 864
Stone, The Dangerous Age in Men, 862
Sutton and Sutton, Diseases of the Skin, 866
Thoma, Clinical Pathology of the Jaws, 286
Thomas, Lincoln's New Salem, 126
Thomson and Thomson, Annals of the Pickett-Thomson Research Laboratory, Vol. X, Mon. XVI, Part II, Influenza, 127
von Verschuer, Erbpathologie, Ein Lehrbuch für Ärzte, 285
Wertham and Wertham, The Brain as an Organ, 434
Wiener, Blood Groups and Blood Transfusion, 866
Wiggers, Physiology in Health and Disease, 429
Wilmer, Atlas Fundus Oculi, 862
Worcester, Hygiene for Freshmen, 125
Sex-Hygiene, 129
The Care of the Aged, the Dying and the Dead, 866
Zinsser, Rats, Lice and History, 869
Reznikoff, P., Foot, N. C., and Bethea, J. M., etiologic and pathologic factors in polycythemia vera, **753**
Richard, E. K., *see* Lloyd, J. J., **119**
Richter, H. A., serial electrocardiograms in coronary thrombosis, **487**
Ringworm of scalp; curability, etc., **364**
Riven, S. S., dermatitis gangrenosa; diabetes mellitus complication, **550**
Robinson, C. S., Derivaux, R. C., and Hewell, B., factors affecting appearance and duration of glycosuria, **795**
Roth, G. M., and Brown, G. E., *see* Barker, N. W., **36**
Rupture, spontaneous, of esophagus in syphilis, **80**

S

SALPINGITIS, acute, and acute appendicitis, sedimentation time as differentiation aid in, **383**
Sampson, H. L., *see* Brown, L., **325**
Sarcoma, spindle cell, of pancreas, **784**
Scalp ringworm; curability, etc., **364**
Scarlet fever effect upon the heart, **352**
Schonberg, I. L., *see* Eller, J. J., **240**
Schwab, R. S., and Weiss, S., neurologic aspect of leukemia, **766**
Sclerosis, coronary, four-lead electrocardiogram in; consecutive patients' series, **833**
Scott, J. P., and Waltz, A. D., congenital cysts of lung, **788**
Sedimentation time as differentiation aid in acute appendicitis and acute salpingitis, **383**
Selye, H., *see* McEuen, C. S., **423**
Serum volume, measurement of, 751
Short, D. M., *see* Crimm, P. D., vitamin A content of human liver, **571**
Shumway, N. P., Williams, T. L., and Fetter, F., *see* Duncan, G. G., **403**
Siegel, A. E., treatment of chorea, 145
Simmonds' disease, multiglandular syndromes resembling; case report, **245**
Skin tuberculosis; recent progress in theory and practice, 590
Smith, C., *see* Hueper, W. C., **778**
C. T., Harper, T., and Watson, A., sedimentation time as differentiation aid in acute appendicitis and acute salpingitis, **383**
H. L., *see* Magee, H. R., **683**
R. E., *see* Wedd, A. M., **690**
Snake venoms, ultraviolet rays' effect on, **520**
Sodeman, W. A., recent studies on fat metabolism, 134
Sodium salts and suprarenal extract use in Addison's disease, **419**
Spectra of hemoglobin derivatives, 154
Spinal shock, reflex thresholds in cat during, 303
Sputum study in pulmonary asbestosis, **44**
Staphylococci, studies on, 436
Staphylococcus bacteriophage, polyvalent, clinical application of, in bronchoscopy, **91**
Starch and dextrose effects on glycemia and glycosuria in diabetics, **545**
Stealy, C. L., chronic granulocytopenia of 5 years' duration with recurrent acute attacks; case report, **633**
Stephens, D. J., acute eosinophilic leukemia, **387**
Sternal puncture, diagnostic value of, in clinical hematology, **515**
Sterols, Liebermann-Burchard reaction velocities of, 302
Stewart, C. M., *see* Gilbert, E. W., **532**
Stieglitz, E. J., migraine physique, **359**
Stokes, J. H., and Garner, V. C., skin tuberculosis; recent progress in theory and practice, 590
Strauss, M. B., etiology of "alcoholic" polyneuritis, **378**
Streptococcus pneumonia, parenteral liver therapy in, **374**
Structures, adjacent, relations with, oto-rhino-laryngology, 876
Strychnin and quinidin in treatment of premature contractions, **206**
Sulphur metabolism; cystinuria case study, 301
Suprarenal extract and sodium salts' use in Addison's disease, **419**
Syndromes, multiglandular, resembling Simmonds' disease; case report, **245**
Syphilis, spontaneous rupture of esophagus in, **80**
transmission, factors conditioning, by blood transfusion, **808**
Syphilitic heart disease, electrocardiographic changes after potassium iodid in, **681**
Sutherland, C. G., radiotherapy, 742

T

TECHNIQUE, standardized, for blood sedimentation test, **102**
Temperature determinations in female pelvis during diathermy, **555**
Therapy, foreign protein, I, **95**
Thevetin, action of, a cardiac glucosid and clinical application, **193**
Thomsen's disease (myotonia congenita), **714**
Thrombo-angiitis obliterans, pain in; clinical study of 100 consecutive cases, **819**
Thrombosis, coronary, aërial electrocardiograms in, **487**
and its effect on heart size, **858**
Thyroid, diet and dinitrophenol, obesity treatment by; 106 outpatients, **86**
Thyroidectomy, total, treatment of heart failure and angina pectoris by, 727
Tissue extracts' effect on muscle pains of ischemic origin (intermittent claudication), **36**
Toxemia of pregnancy patients, failure to find pressor and antidiuretic substances in, **615**
Traut, E. F., *see* Carter, J. B., **206**

Tuberculosis, early pulmonary, endogenous origin of; anatomic view of clinical diagnosis, **253**
pulmonary, treatment of, **325**
renal, variations in blood pressure in, **803**
skin; recent progress in theory and practice, 590
susceptibility to: race or energy level? **330**
Tumor-bearing rats, histologic changes in adrenals of, **423**
Tumors, ovarian, 581

U

Ultraviolet rays' effect on snake venoms, **520**
Undulant fever, pneumonia in; 3 case reports, **483**

V

Vascular disease, advanced peripheral, alternate suction and pressure in treatment of, **305**
response sensitivity to epinephrin after plasma injection from nephritic patients, **371**
Venesection, early response to, on so-called bloodless venesection, **813**
Vertebrate retina, nerve impulses in single fibers of, 751
Vitamin A content of human liver, **571**
Von der Heide, E. C., and Myers, G. B., *see* McKean, R. M., **702**

W

Wagener, H. P., retinitis pigmentosa, 297
Waltz, A. D., *see* Scott, J. P., **788**
Warwick, M., obtaining permissions for autopsies, **341**
Watson, A., and Harper, T., *see* Smith, C. T., **383**
Wedd, A. M., and Smith, R. E., observations on prognosis in angina pectoris, **690**
Weinstein, A., multiglandular syndromes resembling Simmonds' disease; case report, **245**
Weiss, M. M., *see* Horine, E. F., **858**
S., *see* Schwab, R. S., **766**
Williams, T. L., Shumway, N. P., and Fetter, F., *see* Duncan, G. G., **403**
Wilson, J. A., parenteral liver therapy in streptococcus pneumonia, **374**
Wintrobe, M. M., and Landsberg, J. W., standardized technique for blood sedimentation test, **102**
Wishnofsky, M., and Kane, A. P., dextrose and starch effects on glycemia and glycosuria in diabetics, **545**
Wright, D. O., macrocytic anemia and hepatic cirrhosis, **115**

Y

Yawger, N. S., is there a "moral center" in the brain? **265**

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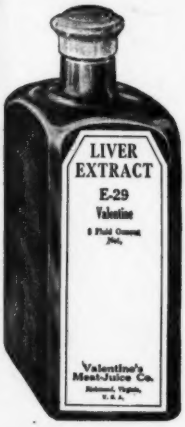

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[1] Science, 73, 243 (1931)
[2] Jour. Nutrition, 6, 179 (1933)
[3] Klin. Wochschr., 12, 1241 (1933)
[4] Science, 78, 609 (1933)
[5] Va. Med. Monthly, Jan. (1931)

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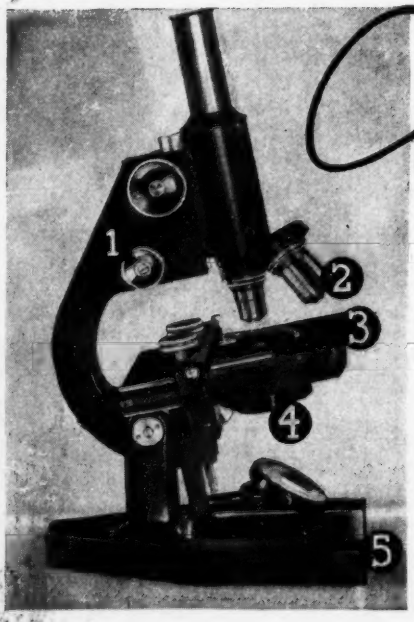

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THESE STRUCTURAL FEATURES

1. A fine adjustment is built not for ten years, but for a lifetime of service. To verify this, the Bausch & Lomb fine adjustment was run day and night on a lathe for an equivalent period, and still showed no wear.
2. Objective's lenses are mounted in threadless cells and parfocalized by a special patented method.
3. The stage measures 115 mm. by 130 mm.
4. A full-ring condenser holder with clamp will still give positive centering 50 years from now.
5. Compare the balanced, stable base with any other base. Examine the entire exterior finish and the plated parts. In fact, line up a group of microscopes on a table—stand back 10 feet—then notice how the Bausch & Lomb instrument dominates, symbolic of superior craftsmanship.

For complete details write to Bausch & Lomb Optical Co., 649 St. Paul Street, Rochester, N. Y.

Bausch & Lomb